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OF THE NEW YORK ACADEMY OF MEDICINE

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Original Articles

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PRESIDENTIAL ADDRESS

CENTENNIAL CELEBRATION

1847—CENTENNIAL OF THE ACADEMY—1947

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THE NEW YORK ACADEMY
OF MEDICINE

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THE CENTENNIAL CELEBRATION OF THE ACADEMY

GEORGE BAEHR

President, The New York Academy of Medicine

IN this, the one hundredth year since the founding of the Academy, it is the solemn duty of its officers and of all devoted Fellows to review the history of the institution which we have inherited from our predecessors, so that we may renew our faith in its important mission and look forward with hope and confidence to the years of public service which lie ahead. Although its beginning was most humble, a room over a coal yard at 175 Wooster Street with the imposing name, Convention Hall, the spirit of the enthusiastic Founders of the Academy was high and noble. They dedicated themselves to the establishment of an institution for the improvement of medical education, the advancement of the public health, the elimination of quackery and malpractice and the instruction of the public on matters of health and hygiene. In spite of the primitive state of medicine in the year 1847, the magnificence of the spirit which moved the 185 Founders and the appeal which their high motives made to the medical profession and to the general public in that year can be judged from the fact that the First Anniversary

* Inaugural Address delivered at the Stated Meeting of the Academy on Thursday, January 2, 1947.

Oration which was delivered in the Broadway Tabernacle by Dr. John W. Francis, second President of the Academy, on November 10, 1847, attracted an audience of more than 2500 persons. This may well be regarded as the Academy's first and most popular Lecture to the Laity.

At the first meeting of the Academy on January 6, 1847, the library was started with a gift by Dr. Isaac Wood of three volumes of Paine's Commentaries. From this small start, and in spite of many decades of discouragingly slow progress, the goal was reached within our generation, so that we find ourselves today in the possession of one of the great medical libraries of the world, housed in one of the most beautiful and impressive buildings in New York, with its commodious meeting halls and conference rooms. In this modern home the scope and importance of the Academy's daily work for the advancement of public health, medical education and public instruction far exceed the most ambitious dreams of the Founders.

The Academy's Centennial Celebration will open on the sixth of March, with an assembly of the Fellowship and the friends of the Academy. As we do not have a hall in the Academy building large enough to hold the entire Fellowship, we have engaged the grand ballroom of the Waldorf-Astoria for that evening. I am priveleged to announce that The Centennial Discourse will be delivered on that occason by Professor John A. Ryle, formerly Regius Professor of Medicine at Cambridge, England, and now head of the Institute of Social Medicine at Oxford. His address will be on "Social Pathology and the New Era in Medicine."

We owe the rare opportunity of his visit to the Academy on this historic occasion to the kind assistance of the Rockefeller Foundation.

Following the opening dinner meeting of the Fellowship, we have planned a series of activities in the Academy building which will continue daily throughout the months of March and April. Each of the eleven Sections of the Academy will celebrate the Centennial with a dinner of its own members followed by a memorable meeting in which eminent authorities in the specialty from New York and other parts of the country or from abroad will participate. Each of the Academy's Standing Committees has arranged for a three day Institute or round table conference devoted to Post Graduate Medical Education, Public Health, Social Medicine, Hospitals, and Medical Libraries. In addition to Fellows and invited guests, representatives of the medical schools and

of governmental and voluntary agencies in each of these fields will participate.

Various affiliated clinical and scientific societies such as the Harvey Society, the Society for Experimental Biology and Medicine, New York Heart Association, New York Diabetes Association, New York Roentgen Society and others are planning to hold special meetings during March and April in the Academy to commemorate the Centennial. The Academy has also offered its hospitality to other sister academies and societies in this area such as the New York Academy of Sciences and the New York Chapter of the American Chemical Society.

An historical exhibit of the Academy and its role in medical progress over these one hundred years is being assembled, which will be on view in the Academy throughout March and April. Among other historical material of rare interest, it will include the portraits of the thirty-nine past presidents and many other distinguished Fellows who contributed to the advancement of the medical sciences during the past century.

With the help of the City Planning Commission, the Department of Hospitals, the United Hospital Fund and the Hospital Council of Greater New York, an exhibit is also being assembled dealing with the history of the older Municipal and voluntary hospitals of the City, at which plans for their post war development will be shown. At this exhibit on hospitals, a master plan for the future hospital development of Greater New York will be revealed to the medical profession and to the public for the first time.

Meanwhile, throughout the City, the Academy's Centennial will be celebrated by special public exhibits on medical and historical subjects at the Metropolitan Museum of Art, the New York Public Library, the New York Historical Society, the Museum of the City of New York and at private art galleries which possess famous prints collections and other memorabilia on the medicine of a hundred years ago. As a special feature of the celebration, your president will broadcast over a nationwide hook-up an address on "A Hundred Years of Medical Progress."

The Academy's special Committee on Medicine and the Changing Order has planned a three day symposium on Social Medicine and the related changes in medical practice and medical education which will be necessary to make the full benefits of modern preventive and curative

medicine available to all people. The occasion will also be utilized to make public announcement of the release and publication of this important Committee's complete report and recommendations which, it is hoped, will have an important influence upon future changes in the methods of medical practice and medical education in this country.

I cannot close this brief forecast of the events of the Centennial year without mentioning the publication by the Committee on Medicine and the Changing Order within the last two years of ten monographs covering almost all the present day problems concerned with medical care, from Hospitals and Nursing to Medical Insurance and Medical Education. The monumental labors of this distinguished Committee for almost four years under the untiring leadership of its Chairman, Dr. Malcolm Goodridge, and of its Secretary, Dr. Iago Galdston, will culminate in the publication in March of the volume embodying its Report and Recommendations. I must here record our indebtedness to the Commonwealth Fund, the Josiah Macy Jr. Foundation and the Milbank Memorial Fund for the financial support of this most important undertaking in the history of the Academy. I recommend the Final Report to you for careful reading.

Finally, I am pleased to announce that the compilation of a comprehensive History of The New York Academy of Medicine, which Dr. Philip Van Ingen generously undertook almost two years ago, is approaching completion. This interesting volume will be ready for publication and distribution during this Centennial year.

In all the commemorative exercises of the Centennial, the major theme will be the relation of modern medicine and its various clinical and scientific branches to the changing social order of today. The celebration will be founded on the premise that the accomplishments of the past cannot be accepted as virtues except as they may be used as a background upon which to build a new pattern of future service to the medical profession and to the people of this City and of the Nation.

By the time the celebration is ended, the Fellowship and the public will have been made fully aware of the role which the Academy has played in the life of this City and of the Nation over the last hundred years, and of its potentialities for continued service to the people and to the medical profession. The Fellows of the Academy have assumed the burden of a great responsibility. I take this occasion to appeal to the general Fellowship for help with the labors which lie ahead. We also

need your assistance and that of your lay friends and patients in carrying the financal load which our library and the work in the various fields of public service entail. Knowing our history, you can point with satisfaction to masterly accomplishments of the Academy in the reduction of maternal deaths, the establishment of a national quarantine service, the sanitation of cities, the abolition of the obsolete coroner system, the establishment and improvement of vital statistics, the development of a Standard Nomenclature of Disease that is now used in almost every medical school and hospital throughout the United States and to many other public services too numerous to mention.

As with all institutions at this time, salaries have climbed and costs of all kinds have mounted well beyond our present income, so that the past year has ended with a deficit of $40,000. We have reluctantly raised our dues for 1947 25 per cent, but I would have you remember that the dues from Fellows and library subscribers make up less than one-fifth of our expenditures. The other four-fifths must come from income on the endowments and bequests which the fellows and friends of the Academy have contributed in the past. The Academy needs an additional income of $50,000 in 1947 and an increase in its endowment of $1,000,000. Let each of us ask himself the question, "What can I or my friends do for the Academy either in direct services or in some measure of financial assistance?" The shelves of our library stock rooms are a solid mass of books, in many places two rows deep, so that the library attendants, with the best of good will, can no longer serve you as promptly as they did in the past.

I am greatly honored to be reelected as your President for another two years, and shall do my utmost to deserve your confidence.

In September, Dr. Herbert Wilcox retired from the Directorship after having served the Academy devotedly and most efficiently since April 1939. We shall long miss his kind help and his patient leadership. Upon his retirement, Dr. Howard Craig took over the administrative responsibilities of the Academy. Under his resourceful direction and with your help, the Academy will carry on in the tradition of the last one hundred years.

THE ACADEMY CENTENNIAL

HOWARD R. CRAIG

Director, The New York Academy of Medicine

THE first hundred years of any institution, such as The New York Academy of Medicine, may well be, as the saying goes, the hardest. The completion of that century, covering its metaphorical weaning, toddling and adolescence, may be the product of mere survival, or it may be the result of a vital, purposeful career. The late Dr. William W. Herrick in his Presidential Address of 1945 stated that any institution was but the lengthened shadow of a man. Little did Stearns, Mott, Purple, Francis, Janeway, Delafield, Jacoby and the others realize the length or the substance of their shadows, for they builded solidly on service to the ill, to their confrères, and to the public well-being.

During the Centennial Celebration of The New York Academy of Medicine in March and April, 1947, this note of historical retrospection will be amplified and developed in the forthcoming History of the Academy which is nearing completion; in the Section meetings; and in exhibits both at the Academy and at various coöperating institutions scattered over the City.

The present activities and functions of the Academy through its Library, its Sections, and its Standing Committees on Medical Education, Medical Information and Public Health Relations, are common knowledge though sometimes not as thoroughly appreciated by the Fellows as by physicians in other cities and states.

The Institutes sponsored by the Committees on Library, Public Health Relations, Medical Education and Social Medicine, will be in the nature of three day round-table working conferences arranged particularly for workers and other persons interested in those particular fields. The subject matter and dates for these Institutes have already been announced and the names of the discussion leaders will be forthcoming shortly.

Invitations for the Centennial Celebration Dinner on March 6, 1947 at the Waldorf-Astoria Hotel has been mailed to the Fellows. Each Fellow is urged to make his reservations as early as possible.

RECENT ADVANCES IN CANCER RESEARCH*

The Ludwig Kast Lecture

PEYTON ROUS

The Rockefeller Institute for Medical Research

IN 1913 H. G. Wells remarked, in *The New Machiavelli*, that to organize a laboratory expressly for cancer research was like issuing a license for a bath chair to scale the Himalaya Mountains. Yet already several such licenses had been issued; the laboratories were working valiantly; and now in 1946 the bath chairs are far up the slope of the mountains, and all about them, some in front, some behind, are other motley vehicles, not to speak of solitary climbers legging it along. The present is a good moment to speak of advances made.

Experimental cancer research is less than 50 years old, even younger than bacteriology; a few of the men who began it are still active. It got off to a start when the rewards of the close observational study of human cancer had become small. Then for the first time medical scientists paid attention to the fact that animals have tumors too—a fact previously known for some while. With the demonstration that these growths are true neoplasms and the maintenance of a few by transplantation, things got under way. At first hopes ran high that the cause of cancer would be found soon, but then it became clear that the transplanted tumors carried the secret along with them in host after host. Nothing could be procured from the tumor cells that would cause other growths, and anything killing them, in even the least disturbing of ways, brought the neoplastic process to an end. Furthermore, the transplanted tumors failed to call forth any resistance on which attempts at cure could be based in the human being; the new hosts reacted to the grafts merely as composed of tissue foreign to their bodies, not as tumor tissue. The cultivation of cancer cells *in vitro*, though occupying many workers, contributed no deep-going enlightenment, and until 1915, when tumors were purposely

* Presented at the 19th Graduate Fortnight of The New York Academy of Medicine, October 7, 1946. From the Laboratories of The Rockefeller Institute for Medical Research, New York.

induced by means of tar, workers were unable to get at the conditions determining the occurrence of neoplasms. Until then, observations on the "precancerous states" of man had been the sole reliance of the investigator, since the spontaneous growths of animals had been too far along when first encountered to be informing. But now at last the conditions leading to cancer could be got at experimentally.

What are the recent advances? It will doubtless be agreed that when a fact or idea first attains recognition by scientists, this constitutes a recent advance though it may have been decades in the making. Perhaps the largest step forward of the last few years has been the very gradual comprehension, gained incidentally to the experimental production of tumors, that cancer is not a separate neoplastic entity, does not stand off by itself, but is merely one amongst the immense group of the true neoplasms, all these being expressions of a single general principle, the neoplastic principle as one might call it, however widely they differ in cellular make-up. To the practitioner this may seem an academic ruling; he knows but too well that every sort of tumor has its special characters, and even each growth an individuality of its own. For him the neoplasms cannot but be heterogenous diseases, and for the safety of his patients he must continue to look upon them as such. Until a little while ago experimenters did so too, and indeed when they first found themselves able to produce tumors they concentrated on getting cancers for study, disregarding almost entirely such other growths as happened to be elicited; they even applied the term "carcinogenic" to the agents which induce tumors, as if these gave rise to malignant epithelial tumors and no others—a usage which persists to this day. Now every investigator realizes that these agents call forth not only cancers but growths of all the main categories dealt with in the textbooks on human neoplasms. A single chemical carcinogen may elicit the whole diverse array, the precise kind of tumor which appears in a given experiment depending upon the kind of cells on which the agent is brought to bear. Not only this, but they call forth the leukemias as well, and almost insensibly these latter have come to be acknowledged as within the neoplastic fold. Every now and then leukemias have been encountered in animals, or elicited, consisting of cells which give rise to tumors if injected into the connective tissue instead of into the blood. The investigator who tackles the cancer problem really tackles the tumor problem as a whole, and he can hope by studying one growth to learn something

about those of many sorts. From here on, in the course of this survey, the terms "cancer" and "tumor" will often be used interchangeably.

Long before the first neoplasm was induced in an animal physicians had good reason to be aware that there are agents in man's environment which cause him to have tumors. But nobody had any conception of how widely distributed these agents are, or of how insidiously they work in some instances, or what a great host of them there can be—for chemists are now synthesizing new ones all the time to learn how they act, and more will be encountered as unforeseen hazards of new industrial processes. In the last few years we have come to know them in bewildering variety. We literally spend our lives amidst them; the very sunlight gives rise to cancer, and the only reason any of us go free from the disease is because the action of most carcinogens is occasional or weak.

Two British workers, the Kennaways, have found on scrutinizing English statistics that cancers of the skin, mouth, throat, esophagus, and stomach, all the way to the pylorus, are more frequent the lower the social scale of the human individual. Evidently the skin of poor people is more liable to be injured in ways that bring on cancer than of people in easy circumstances, and what they eat and drink is in all probability more likely to contain carcinogens. The thought that we may take in such substances with our food is disturbing. Recently it has been discovered that rats fed 2-acetaminofluorene develop tumors after a while, here, there or yonder, at spots far distant from the digestive tract, and some of the azo dyes have proved capable of giving rise to cancers of the liver when they are fed to rats placed on special diets. One such substance has been used in the past to color butter. They are harmless when given with certain food stuffs, and many workers attach great significance to this fact, though others discount it, pointing out that the dyes cannot make the liver cancerous unless they reach this organ, and that they become so strongly adsorbed to certain food stuffs as to be carried intact through the intestine, while in other instances they are degraded and rendered harmless by the bacterial flora of the gut, a flora which differs with the character of its contents. However all this may be, the findings to the present, and the fact that certain hydrocarbons are carcinogenic, have together suggested the possibility that the eating of superheated fats, such as may be formed when frying is bungled, may be responsible, at least in part, for gastric cancer. The evidence

on this point is still equivocal, despite much experimentation.

A far more difficult problem than the carcinogens round about us—since these can be warded off in proportion as we perceive them—is that of carcinogenic agents arising within the body. There are reasons to suppose that they often do so. Some years ago the fact was brought out that tar produced by heating human skin may induce skin cancers when painted on the backs of mice. Of course this does not justify the conclusion that the skin elaborates tar under natural conditions: one might almost as easily suppose that because the body contains hydrogen, oxygen, and nitrogen, it produces fuming nitric acid. But gradually, as new hydrocarbons capable of inducing tumors have been synthesized, it has become plain that some of them are nearly related chemically to substances normally present in the organism, methylcholanthrene for example, almost the most powerful of chemical carcinogens, having a close structural relationship to cholic acid. Also in the last few years the discovery has been made that extracts of some diseased human tissues are capable of producing tumors in animals. The Negro miners of the Bantu race in the Witwatersrand of South Africa nearly all have abnormal livers; hepatic cancers are frequent amongst them; and extracts of their livers are capable of causing sarcomas when injected into the subcutaneous tissue of mice, and of evoking both papillomas and epidermoid cancers when painted on the skin. It might be argued that the chemical procedures employed in obtaining the extracts have resulted in the production of substances not existing naturally; but control extracts made in the same way from the normal livers of Europeans have a carcinogenic action less frequently. Furthermore, Schabad, who did the first experiments of the sort described, produced sarcomas in mice by the injection of mere benzene extracts of cancerous human livers. The fact that some extracts of normal livers have a similar effect does not lessen the significance of Schabad's finding; for, as already stated, it is not the presence of a carcinogen but its presence in effective quantity which determines whether a tumor will arise. The recognition of endogeneous agents and conditions, developing within the organism and capable of causing tumors, is one of the pressing tasks of the day.

For some years it has been known that certain normal substances, namely hormones, may give rise to tumors when they act too forcefully, as when they are injected in quantity over long periods of time. They are not true carcinogens themselves, but are indirect in their influence,

bringing about such pathological states in the tissues they affect, getting the cells into such a disordered condition, that some of them undergo neoplastic changes after a while for reasons unknown. Repeated injection into mice or rats of the estrogens, for example, may render the tissue of the mammary glands so abnormal that cancers eventually take origin from it, and not only may such growths be thus produced but uterine carcinomas also, and lymphosarcomas, leukemias, testicular and pituitary neoplasms and bone tumors. It has become plain of late that most of the hormones influence other organs in addition to those to which they are obviously dedicated, and nobody knows to what kinds of tumors they may not give rise next if administered in sufficient quantity.

There is an obverse to these findings. Reducing the action of hormones may mean the prevention of certain tumors. It seems possible that enough estrogens may be elaborated within the bodies of some supposedly normal women to bring about the mammary disturbances out of which cancers come. If this is the case steps can be taken to lessen or combat the influence of these substances and the growths thus be warded off.

For nearly 75 years doctors have been aware that many cancers arise where there is chronic disturbance of the tissues, at flexures of the intestine for example, and now the accumulated evidence warrants the conclusion that this is the rule for tumors in general, that they appear only where pathological changes have taken place. Yet mere chronic inflammation is not enough in itself to cause growths; if that were the case, epidermoid carcinomas would arise wherever lupus existed, and cancer would follow upon every leg ulcer present for years. Some special factor there is which precipitates the neoplastic change. Ordinary histological techniques have failed to disclose its character; they are bankrupt in this connection. But of late, new methods have been devised, notably that of Caspersson, a Swedish worker. He has utilized ultraviolet rays of special wavelengths to take photographs of microscopic sections of tissue, and has thus obtained detailed pictures which tell large new facts about the happenings in cells.

At the time when neoplastic changes first appear in response to a carcinogenic agent the tissue acted upon is in a hyperplastic state. But often the hyperplasia is secondary to injury—as for instance in skin injured with Roentgen rays; and certain workers, notably Haddow of the Royal Cancer Hospital in London, have concluded that the cells

become neoplastic while they are faring badly and that the chemical carcinogens act through the depression of cellular activities that they bring about. The injection into animals of some of these substances causes transplanted tumors to grow more slowly, and knowing this fact a European surgeon, just before the War, actually painted operable human cancers of the skin with a powerful carcinogenic hydrocarbon, ignoring the danger that other growths might arise later on as a result of its action. He reported that the tumors disappeared, and in the present state of Europe the end-results of the treatment may never be known. Haddow himself has synthesized numerous hydrocarbons nearly related chemically to those of carcinogenic sort, hoping to obtain some which would check established tumors while giving rise to none on their own account. His results in animals encourage further work and he has now begun clinical trials on inoperable cases. Laboratory observations made in our own country during the War on the effects of the nitrogen mustards to retard cell activity have led to the utilization of such substances in the treatment of lymphoid tumors and leukemia in human beings. There cannot be too many well-reasoned efforts such as these.

What can the cause of tumors be, the actuating cause which keeps them going? One favorite idea went out the window during the first years of experimentation with carcinogenic agents, the idea that cells run amuck and form tumors because of a relaxation of some governing influence exerted by the organism, which had kept them in order previously and all doing what they should. On painting the skin of an animal at different places successively with a chemical carcinogen, it has been found no easier to induce a second tumor, or a third or a fourth, than the one which had arisen at the spot painted first; if the body really exercises a control this is as tight as ever. The conclusion that tumor cells are not mere ordinary cells which have seized an opportunity to go on the loose, but differ from them in some distinctive way—a way yet to be ascertained—underlies all the present-day searchings for chemical traits peculiar to cells in the neoplastic state. The hope that they may elaborate some specific antigenic substance and thus provide a serological test for the presence of a neoplasm goes back to the first years of immunology. Very recently a distinctive antigenic substance has been demonstrated to exist in the Brown-Pearce rabbit carcinoma; but further work has shown it to be peculiar to this neoplasm, quite different serologically from another antigen encountered in a

second kind of epidermoid carcinoma of the rabbit. On the basis of these findings one might perhaps look forward to a galaxy of blood tests, each for some tumor of special sort, but not to a single test which would help in the generality of human instances, those in which the doctor wants to know whether there is any tumor at all in his patient, its precise nature coming afterwards. And even the possibility of special tests is problematic, since in rabbits carrying the tumors above mentioned the antibody formation essential to a serological reaction often fails to take place, although the tumors themselves regularly contain the specific antigen.

Most of the agents which are effective in producing tumors, the Roentgen ray and Bilharzia ova, to cite extreme examples, cannot possibly be the actuating causes of the growths. Their part is played when they have produced neoplastic change; the tumor flourishes on its own, just as a fire does which has been kindled in any one of a myriad ways. But the fact that certain hydrocarbons have proved capable of inducing tumors has led investigators to ask whether substances having similar effects may not be continually formed within cells after these become neoplastic, and maintain them in their abnormal state. Even if this is not the case a knowledge of precisely what the synthetic carcinogens do should prove broadly enlightening. Gifted chemists are now concerned with these possibilities, trying to learn whether there is not some radical or bond or configuration common to carcinogenic molecules which is responsible for their singular effect on the cell. The most widely different carcinogens may give rise to growths of identical sort.

Large opportunities for studies on tumor causation have been provided of late through a feat of the geneticists. By mating mice, brother to sister, year after year, for as many as fifty generations they have untangled the hereditary traits which exist interwoven in the ordinary animal. They are now in possession of breeds of mice consisting of individuals which are not only homogeneous, in that their normal tissues, and their tumors as well, can be transplanted from one to another as successfully as if transferred within the same organism, but which exhibit special characters that are ordinarily obscured by a mixed inheritance and hence find expression only now and then. Some of the pure-bred strains of mice have striking liabilities to spontaneous tumors of one sort or another, while others have equally remarkable freedoms from these growths. Nearly every animal of certain breeds may develop

lung tumors, or liver tumors, or leukemia, or every ageing female may have mammary cancer, whereas in other strains such neoplasms never appear. And back of the primary tumor liabilities there may be secondary ones; an animal escaping the mammary carcinoma which kills most individuals of its strain may in all likelihood die of leukemia later.

What are the reasons for these differences? At first it was supposed that the various tendencies to tumors are hereditary, passed on through the chromosomes. For most of them this may indeed be true. But a worker in Holland and others at Bar Harbor, Maine, who studied crosses between mice of strains having marked and slight liabilities respectively to mammary cancer, found simultaneously that the tendency to such tumors is handed down through the mother. There followed startling discoveries by Bittner, one of the Bar Harbor group. He took young mice of strains highly liable to mammary cancer away from their mothers as soon as they were born; had them suckled by females of a strain with no such liability; and found that thus they were rescued from having mammary cancer in later life. By carrying out the experiment in the opposite direction the tendency to mammary cancer was conferred upon breeds not having it ordinarily. The tendency is passed along from one generation to the next by something in the mother's milk, the "milk factor" as it is now called. A single nursing just after birth is enough not only to establish the factor in the young female itself but in its descendants as well. And most important, whole races of mice can be rescued from having mammary cancer by preventing the milk factor from reaching the original mother of the race.

The factor does not produce its effect at once. It somehow reaches the mammary tissue from the gut, increases in quantity as the glands develop, and when the mouse grows old, one adenocarcinoma or several make their appearance in the breast tissue. This happens in practically every individual of some breeds. Yet nothing can be got from the mammary glands, or from the cancers, which will cause tumors directly on injection into other ageing individuals, only the milk factor, though this in great amount. Titrations have shown that one-millionth of a gram of mammary tissue yields enough of it, on extraction with salt solution, to confer the tendency to mammary cancer on an endless series of animals. A great deal has been found out about the factor in recent years and everything, its size, its physical character, its antigenicity, its continual increase in association with living tissue, its

infectivity—for it sets up what must be regarded as a postnatal infection —all puts it in the category of the viruses save the fact that it does not induce disease directly. The most reasonable explanation for the way it works is that it is a harmless virus, thriving and increasing in the mammary tissue, and varying to become a tumor-producing virus when its cellular environment undergoes pathological alteration, as in the breasts of female mice which have grown old.

These discoveries have caused many surmises as concerns human cancers of the breast. One cannot doubt that within the human species there are hidden liabilities to tumors which find individual expression now and again, but statistics show that only very rarely is the layman's fear justified that there is "cancer in the family." Perhaps, on the analogy of inbred, pure-strain mice, brother to sister matings of human beings during a thousand years might bring out pronounced familial differences as concerns the incidence of tumors; but we can be thankful that, as matters stand, we are a mixed lot. A few workers with the milk factor have lately urged that new-born babies of human families in which mammary cancer has occurred should be taken away from their mothers before they have nursed at all, and be raised on the bottle; but this would be to subject such children to very real dangers because of fears that are ill-grounded in the generality of instances, as the statistical evidence proves.

A great deal of experimentation has been done to learn whether other tumor liabilities in mice besides the mammary are transferred through the milk, but the results have been negative save perhaps in the case of certain leukemias.

The existence of the milk factor has brought new support to the conception that tumors in general may be due to viruses. As is well known, many of the neoplasms occurring spontaneously in chickens yield such agents, with which growths of identical sorts can be produced. Most of the theoretical objections to viruses as the general cause for tumors have been done away with by this finding, but it has not lessened the practical ones. Despite persistent efforts during the last thirty years no viruses capable of directly causing neoplasms have been procured from rat or mouse tumors—the common currency of the laboratory—though a few out-of-the-way growths have yielded them. Lucké has demonstrated that an adenocarcinoma of the kidney which occurs often in the leopard frogs of American swamps is due to a virus,

and the huge papillomatous growths frequently present on the skin of Western cottontail rabbits are also virus-induced, as Shope showed. The papillomas behave like true tumors at the brink of malignancy, and after they have grown for some months metastasizing squamous cell carcinomas often arise from them by secondary changes in their virus-infected cells. These cancers would never happen were it not for the action of the virus, and they appear so soon that the latter rates as the most powerful of known carcinogens for the rabbit. Yet nothing can be extracted from the cancers that will cause such growths, or even papillomas in other individuals; and it is possible that the virus does no more than start off a process with which, like the ordinary physical and chemical carcinogens, it has nothing further to do. The great majority of workers at the cancer problem see little in the idea that the generality of tumors are due to viruses, and recent experimental evidence, into which there is not time to go, speaks against the assumption that agents of this sort, passing from one individual to another, can be their cause. But decisive evidence in the matter may be available soon, for much can be expected of the new techniques for visibility now under development. Already Claude and Porter have obtained pictures of chicken tumor viruses within the cells of the sarcomas they induce, being enabled to do this because the cells spread out so thin in tissue culture as to permit photography with the electron microscope. In a few years at most it should be possible to search the cells of mammalian growths with the same instrument.

One might think that pathologists would now be possessed of a thorough knowledge of the natural history of tumors as result of the diligent observations made on human growths during the last hundred years; but the very definition of a tumor misses the mark, as proven by recent discoveries. The conception has long been axiomatic that a tumor is an autonomous new growth. But Huggins' demonstration that many prostatic cancers, including some which have metastasized, stand still for years or disappear after removal of the patients' testicles shows that even the cells of malignant growths, of cancers ordinarily fatal, are not always truly independent in their behavior. The cells of the prostatic cancers which behave in this way have been spurred on by the male sex hormone elaborated within the gonads and responsible for the normal activities of the prostatic epithelium. When, after orchidectomy, they are no longer thus urged, they cease to proliferate and some-

times they are actually incapable of maintaining themselves. By combatting the influence of testosterone with natural or synthetic estrogens similar results have been obtained.

The significance of this discovery far transcends its practical application; for it means that thought and endeavor in cancer research have been misdirected in consequence of the belief that tumor cells are anarchic. As every medical student knows, the extent to which these cells deviate from the normal varies from tumor to tumor over a wide range, and the greater the divergence the more likely is the growth to be malignant, by and large. It has been known too that the cells of nearly all cancers make some attempt at the customary tasks of normal elements of the same sort, perhaps forming gland-like structures, or making more or less successful attempts to differentiate like the stratified squamous epithelium from which they derived. But no one had realized that neoplastic cells making such attempts at differentiation might also respond in line of duty to normal physiological influences such as the hormones exert. How widely this principle finds expression in the behavior of tumors has yet to be learnt, and how successfully it can be utilized in repressing them. The course of events with prostatic cancer has seemed to justify the expectation that many mammary cancers would dwindle when the influence of the female sex hormone was lessened by removal of the ovaries or by injections of testosterone. The results with women have not been very promising thus far, but the paradoxical fact that cancers of the male breast yield to orchidectomy, or to stilbestrol, is encouraging; for it makes sharply plain the existence of critical factors which have yet to be understood and pressed into service.

A priori one might suppose that the prostatic cancers composed of cells which have lost all the morphological characters peculiar to the gland elements from which they come, which are wholly anaplastic in other words, would be those which would fail to respond to orchidectomy or to the neutralization of the influence of testosterone with estrogenic compounds; and this has turned out to be the case. But Huggins has shown that even the most anaplastic cells still elaborate acid phosphatase, a normal function of the prostatic epithelium. Evidently they are not lost to all good, and it may be possible to find ways experimentally to play upon what might be called their better impulses.

There are other instances in which the formation and the success

of tumors is consequent on the stimulating influence of hormones. Certain testicular neoplasms of mice will not grow after transplantation unless the new hosts are injected with estrogen. A few years ago it was noted that uterine myomas develop in guinea pigs thus injected, and Lipschütz, working in Chile, has now demonstrated that testosterone will prevent the growths from appearing. Whether this has a practical bearing remains to be seen.

It is a curious fact that while hormones play a large role in tumor production and behavior little has been found as yet which the vitamins do. This is not for lack of tests with them.

The dependence of some tumors on hormonal influences for success justifies the inference that the change of a normal cell to a tumor cell does not necessarily mean that a growth will arise; and proof in the matter has been accumulating recently. Most of the tumors which appear on skin exposed to carcinogenic agents require favoring conditions if they are to grow, and the carcinogen itself provides these by setting up a chronic local inflammation productive of hyperplasia. After the carcinogenic applications are stopped many or all of the induced growths, including squamous cell carcinomas, may disappear rapidly as the local disturbance wears off. The course of those growths that progress and later prove highly malignant is often hesitant in the beginning. If the caloric intake of mice is cut down somewhat, so that the animals appear fit instead of fat, though slightly smaller than usual, the carcinogenic hydrocarbons induce relatively few tumors on their skin and these appear much later. This is not because the agents have failed to bring about neoplastic changes; for if the animals are full-fed later, tumors rapidly start forth although the carcinogen has not again been applied. The "spontaneous" pulmonary growths to which mice are liable can also be prevented from appearing by moderate restriction of the food intake. It would be worth while to know whether the incidence of cancer has fallen off in the starving populations of Europe. At the moment much work is under way to learn whether modifications of the diet which involve no caloric reduction will hinder tumor growth.

In proportion as a tumor continues to grow, cutting down the food is less effective in hindering it. This is in part because the best equipped cells tend to come to the fore as proliferation goes on, and in other part because secondary neoplastic changes, superimposed on the first and always for the worse, may render the tumor more aggressive. Often

cancers seen in the clinic are the end result of a series of untoward happenings and have been "babied along" by this influence, or that circumstance. It is no accident that most of the precancerous states observed in man provide conditions notably favorable to cell proliferation. And yet most of the cancers seen by the surgeon are not doing all of which they are potentially capable, as witness the stimulating effect upon them later of trauma, necrosis, ulceration, bacterial infection. Ultimately however, some of them become superior to their circumstances; many cancers grow with exceeding swiftness in their final stages, though the patient wastes. Much has still to be found out concerning the adjuvant influences which make clinical cancers worse. Without doubt some of these influences can be excluded or combatted.

These facts lead on to a conclusion of large practical import, namely, that the cells of not a few malignant growths can be held in check, kept from dividing, if steps are taken while they are in the early, hesitant stage; and to hold them in check is, in effect, to prevent the cancers. The systematic examination with the microscope of human prostates has shown that carcinomas are frequently present in them which never cause trouble. Not only should a tumor be got at early because then it is small, but because then it is different, a far less capable threat intrinsically. Even the smallest details in the previous history of cancer patients, no matter how far back, may prove vital for other human beings, as giving hints about where the chain of events can be broken which leads on to the disease. Too much pains cannot be spent in eliciting such histories. There should be specialists in every cancer hospital whose duty and ambition it is to learn precisely how each patient's tumor has come about. For just beyond such knowledge lies prevention.

Numerous discoveries might be mentioned which perhaps have a greater claim to attention than those here dealt with; the years will show. But at the moment most of these have only the status of random facts, facts with no setting, what might be called knick-knacks of knowledge because how they fit into it is not yet clear. What is the meaning, for example, of the discovery made in France by Lacassagne that Roentgen rays applied in very small amount to the leg muscles of rabbits, at spots where a pyogenic infection has healed a year or two previously, often lead to the appearance of sarcomas? There is more here besides a hint to practitioners of radiology. And what of the finding that general anesthesia with urethane, lasting only a few hours,

is followed by the rapid appearance of multiple lung tumors in mice of the breeds liable to occasional growths of the sort? And why should urethane, though provoking lung tumors in mice, actually hinder the course of human leukemia? Each of these well-attested observations means something, perhaps something large, but no one can say now what it is. Any new fact about cancer is worth while, and the growing heap of knick-knacks assuredly holds treasures. The authenticated advances themselves have been largely episodic in character. Yet there is a feature common to most of them which bodes well for the future; they are not the reward of random strivings but of intent and purposeful head-work. They give the physician good reason to look forward to the day when knowledge of cancer will come to be power.

LYMPHOMAS AND LEUKEMIAS*

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EVERY doctor in practice, no matter what kind of practice he is in, is surely going to see some aspect of that wide range of disease processes that are included in this title, lymphomas and leukemias, for the reason that they can affect any part or function of the body, and can mimic many other diseases. Obviously, therefore, lymphomatous and leukemic disease processes should occupy an important compartment in every doctor's knowledge of medicine. Yet, not only does there seem to be a considerable degree of unfamiliarity with these diseases, bred from a belief that they are too rare to merit much attention, but they seem to connote in many practitioners' minds a particularly bad prognosis in the field of cancer.

My purpose in this discussion is to give to the diseases included in the terms lymphomas and leukemias their proper share of recognition in a program devoted to cancer, about which there is now so much interest and hope, and to show that the prognosis may be far better than is generally assumed.

A few cogent reasons will serve to emphasize the importance of this group of tumors of the lymphatics and blood-forming organs.

1. To a large extent, they strike down persons whose lives are just opening before them—infants, adolescents, and young adults—and thus are of greater economic and social impact than are diseases which affect mainly the aged.

2. They are not so rare. Reports of wards in army and navy hospitals that contained 60 patients with Hodgkin's disease at one time make one realize that here is a real problem affecting largely our youths. Louis Weiner, chief of the statistical division of the Department of Health of the City of New York has kindly furnished figures for the deaths from Hodgkin's disease, lymphosarcoma and leukemia in New York City for the years 1940 to 1945 inclusive. These figures show that

* Given October 10, 1946 at the 19th Graduate Fortnight of The New York Academy of Medicine.

TABLE I—78157 DEATHS FROM MALIGNANT TUMORS IN NEW YORK CITY, YEARS 1940-1945

	Deaths	%
Hodgkin's disease	928	1.2
Lymphosarcoma	1346	1.7
Leukemia	2735	3.5
Total	5009	6.4

to all malignant tumors Hodgkin's disease deaths bore a ratio of 1.2 per cent, lymphosarcoma 1.7 per cent, and leukemia 3.5 per cent. Thus taken together they account for 6.4 per cent of all deaths from cancer or about one case in every 16 (Table I).

3. Their ability to affect any tissue or function of the body means that not only every general practitioner, but every specialist as well, must be prepared to consider these diseases in his decisions about diagnosis and treatment.

4. There is evidence for at least the theoretical possibility of cure of early localized Hodgkin's disease and lymphosarcoma.

5. There is evidence of decidedly worthwhile greater palliation and prolongation of life resulting from precision of treatment methods based on more knowledge of the pathologic anatomy and on close follow-up of patients.

6. These diseases lend themselves well to clinical investigation of cancer and trial of new therapeutic methods. For example, if we can discover the secret of the leukemia cell we may be a long way on the road toward an understanding of the malignant neoplastic process in general.

An example of the way in which trial of new therapeutic agents on lymphomatous disease may yield unexpected dividends was the discovery last winter that nitrogen mustards, known to have palliative effects in varying degrees on lymphomas, especially Hodgkin's disease, could also exert marked palliative effects on anaplastic bronchogenic carcinoma.

7. Last, but not least in the reasons for the importance of these diseases, is the thought that, while in the mind of the practitioner, one of these diseases, when encountered, may elicit only an attitude of sympathy for what he believes to be a hopeless outlook in a rare disease, yet, to the patient who has it, the disease is of prime importance and

its rarity of no consolation. There would be no question of the patient's choice, as between condemnation to one or two years of hopeless invalidism if nothing, or too little is done, and the chance, although not the guarantee, for 3, 5, or perhaps even 10 or 15 years of comparative comfort, if not cure, if his treatment is prompt, and followed up regularly.

These diseases, the lymphomas and leukemias, stand so rather apart in the field of malignant tumors, by virtue of their peculiarities, that it has often seemed to the writer high time that some sort of special institute or hospital be organized to study and treat them.

In dealing with so complex and poorly understood a group of diseases it becomes desirable to formulate a sort of philosophy about them —to keep in mind a general concept as an aid in approaching problems of diagnosis and treatment. At the same time it is not helpful to think of them under the single concept of lymphoblastoma or leukemia. We should want to know in any specific case whether we are dealing with Hodgkin's disease or lymphosarcoma, with mycosis fungoides or myeloblastic leukemia, with polycythemia vera or erythroleukemia.

Although we try to fit each case into a specific category, we have to recognize that borderlines are not sharply drawn. What is today in this patient a case of Hodgkin's disease may 5 years from now prove to have evidence of giant reticulum cell sarcoma. The case that today is one of giant follicle lymphoma, very radiosensitive, and seemingly curable by moderate x-ray therapy, is practically certain in 2 to 10 years from now to be a case of relatively radioresistant reticulum cell sarcoma. In the case that has a generalized lymph node enlargement, with a biopsy showing lymphosarcoma, and with a blood count showing lymphatic leukemia, shall we call the disease lymphosarcoma, or lymphatic leukemia, or shall we compromise and call it lympholeukosarcoma?

Not only do we have these indistinct boundaries between what would otherwise be distinct entities, and not only do we have these transitions, apparently from one condition into another, but we are confronted many times, also, with cases apparently lying on the borderline between inflammatory processes and true lymphomas and leukemias.

It is not at all uncommon to find that there is difficulty both in the clinic and in the pathology laboratory in making such distinctions as between tuberculosis and Hodgkin's disease, Boeck's sarcoid and Hodg-

kin's disease, Boeck's sarcoid and lymphosarcoma, brucellosis and Hodgkin's disease, atypical infectious mononucleosis and lymphosarcoma, dermatopathic lymphadenitis and Hodgkin's disease.

An unusual example of the confusing overlappings in this field is afforded by a patient now under treatment, who in the course of about six years has provided our pathology service with lymph nodes suggesting at one time tuberculosis, another time follicular lymphoma, then specimens from partial gastric resection and liver biopsy diagnosed sarcoidosis, and most recently another lymph node biopsy that showed Hodgkin's disease!

One part of the philosophy of these diseases, then, is to think of them in dynamic and functional terms rather than as static pathologic entities, recognizing that the lability of their tissues and cells of origin—marrow, spleen, nodes and reticuloendothelial system—endows them particularly from the beginning with a property of being in a state of flux, no doubt stimulated or inhibited by various hormonal or other factors, whose modes of action are as yet little known.

Only by reference to these unknown factors of growth stimulation and control can we lamely account at this time for such variations as those which permit one patient with generalized lymphosarcoma to do well for years with a minimal amount of x-ray therapy, while another with no appreciable difference in histology of tumor, or amount of disease, progresses rapidly to fatal outcome.

Another more practical part of the philosophy has to do with the premise that Hodgkin's disease and lymphosarcoma, and particularly Hodgkin's disease, give evidence of arising often in a single focus and that generalization takes place by spread from that initial focus, as in other malignant neoplasms. There is perhaps some basis for a belief that even leukemia may start at one focus, but if so it is never recognizable, until it is a generalized disease. While admitting that in some cases of Hodgkin's disease, and perhaps in the majority of cases of lymphosarcoma, there may be either a multicentric origin, or at any rate such a rapid generalization that it almost amounts to the same thing, yet there does seem to be evidence for the unicentric origin of most cases of Hodgkin's disease and some cases at least of lymphosarcoma.

In Hodgkin's disease, for example, any clinic that has treated a considerable number of cases over a period of 20 years or more can cite cases in which the disease has been treated adequately when fairly early

and regionally localized, and in which there has been long survival and little or no spread of the Hodgkin's process beyond those sites in which it was originally found and treated. A woman who had mediastinal and supraclavicular Hodgkin's disease, treated vigorously for about 3 years, then went for 15 years with no apparent need for treatment, only to have Hodgkin's disease then recur in the mediastinum and after 4½ years eventually kill her by intrathoracic spread, pleural effusion and cardiac failure, but at autopsy there was no sign of Hodgkin's disease below the diaphragm. Thus she had a total course of 22½ years following the first treatment, with persistently regional localization of the disease.

Of course such cases are exceptional, and no doubt may possess some inherent factor that, in addition to the intensive early treatment, tends to inhibit spread of the disease, but at the same time they do support the thesis that Hodgkin's disease or lymphosarcoma may arise in one focus, and that if the original localized disease is in such a location that it is amenable either to complete surgical removal followed by x-ray therapy, or to obliterative roentgen therapy, there should be a possibility of cure.

In contrast with these early localized types we have the cases that still comprise the bulk of what we have to treat, those in which the disease is widespread. This includes, of course, all the leukemias and most of the cases of mycosis fungoides, lymphosarcoma and Hodgkin's disease. Leukemia when diagnosable is always a generalized disease, while the others may have a greater or lesser degree of generalization. The philosophy in these generalized forms is to accept at once the incurability of the process by any means known today, and so to design the treatment as to gain the best and longest palliation. Yet in Hodgkin's disease and lymphosarcoma, the majority of cases when first seen present a setting somewhere intermediate between strict, unifocal localization and universal generalization. Those with a nearer approach to regional localization may do well with fairly intensive local therapy, while those with very widespread disease may have to be treated quite circumspectly.

In this whole field results today in palliation can be much better than they were two decades ago, mainly because of greater knowledge of and consequently search for obscure lesions, the control of which is at least as important, if not more so, to the patient's well-being, as the

control of the more obvious lesions. We no longer think of Hodgkin's disease and lymphosarcoma as diseases of the lymph nodes alone, or of leukemia as a disease of marrow, spleen, nodes and blood alone, but rather as processes that may produce lesions of any organ or tissue.

In order to stress the liability of the lymphomas and leukemias to affect any tissue or organ, let us review some of the data we have.

Skin: Mycosis fungoides—or granuloma fungoides is often spoken of as not an entity, but as merely a cutaneous manifestation of so-called lymphoblastoma. It seems preferable, however, to preserve this name as indicative of a more or less distinct entity. Mycosis fungoides follows a rather distinctive natural course, arising often on the basis of a long standing chronic eczematoid rash, beginning as low infiltrated plaques and progressing to fungating thick cutaneous tumors. The natural history may be very long, upwards of 20 years. Some cases referred to by the French as mycose fungoïde d'emblée arise as tumors of the skin unheralded by the more common preexistent chronic eczema.

In our experience, the earlier cases are diagnosable histologically, while the older cases show a microscopic structure of reticulum cell sarcoma. We have never seen this condition as part of Hodgkin's disease, or leukemia. If it must be regarded as merely part of so-called lymphoblastomas, it should be classed with lymphosarcoma, but its long course is quite at contrast with the average lymphosarcoma, and therefore, from the point of view alone of analysis of 5 year survival curves, it should be kept separate.

One of the clinical varieties of lymphosarcoma that is often mishandled is the type that begins with perhaps only one small insignificant looking, slightly pinkish or purplish plaque in the skin, especially of the scalp. Such a plaque may exist for a year or two before anything else develops, and if not biopsied, may readily be regarded as of no consequence. A few months ago we saw one that had been vigorously squeezed by a physician who thought it was a sebaceous cyst. Yet such an unimpressive lesion may be the first signal of a process that sooner or later will generalize, involving external and internal lymph nodes, spleen, liver, bone, lungs, and other tissues, and eventually kill the patient. However, some of these cases are much less malignant, and can be controlled for long periods by local irradiation.

Hodgkin's granuloma in the skin is relatively uncommon, but may assume bizarre forms, varying from single or multiple plaques and

nodules, non-ulcerated or ulcerated, to broad, diffuse erythematous lesions. In a few cases it may exactly mimic multiple tuberculous abscesses with large irregular necrotic ulcers having serpiginous edges. In some cases there will appear rather rapidly a group of tiny shotty nodules in or just beneath the skin, usually about the upper chest wall. Cutaneous lesions of Hodgkin's disease usually yield well to irradiation.

Herpes zoster is an old acquaintance in this entire field. It has been recognized for many years that herpes zoster has an uncommonly high incidence in cases of lymphoma and leukemia. Occasionally along with classical herpes zoster, there is also a generalized herpes, with varicelliform lesions. Although the literature contains references to examples of cross infection with chicken-pox, we have never found a clear cut instance of such mode of infection.

Leukemic infiltration of the skin is fairly common, especially in lymphatic leukemia. Purpura may exist with or without a reduced platelet count.

A remarkable series of rare cases are what we have called our red Indians. These patients have red, thickened, scaling skin, enlarged lymph nodes and a white blood count suggesting chronic lymphatic leukemia. Apparently some have true leukemia, and some do not, but whether eventually all will become leukemic, we do not know. One such patient, a man, had on two occasions, a remarkable clearing of his skin lesions, and restoration to normal blood count following the administration of estrogens, but later died, apparently having true leukemia. Another such case was reported by Fraser as having a mistaken diagnosis of leukemia, because he had apparently a complete spontaneous remission.

The gastro-intestinal tract may be involved anywhere from mouth to anus by various primary or secondary lesions of the lymphomas, and by various infiltrations or secondary manifestations of the leukemias. Marked swelling and necrosis of the gums, if the patient has a leukemia, has come to arouse always a suspicion that the leukemia may be monocytic.

Hodgkin's disease and lymphosarcoma apparently primary in stomach or bowel have been successfully removed surgically with resultant long survival.

In a series of 36 autopsies in Hodgkin's disease, five showed lesions of the gastric wall, and one had a healed-over duodenal ulcer, the base

of which showed Hodgkin's disease. In a series of 406 proved cases of Hodgkin's disease, about 13 per cent complained of gastro-intestinal symptoms. In many instances these symptoms are caused by intra-abdominal disease that remains extrinsic to the gastro-intestinal tract. The lesions, either intrinsic or extrinsic, may be favorably affected in varying degrees by external irradiation with x-rays, and in some cases may be made to disappear entirely.

The genito-urinary tract is not immune to attack by lymphomatous or leukemic disease. At autopsy leukemia is often found extensively infiltrating the kidneys. Nemenov proposed years ago that in treating leukemia by irradiation, one should first give moderate doses to the kidneys in order to improve their function by decreasing their leukemic infiltration.

Retroperitoneal lymphomatous nodes may so infiltrate as to encase kidneys, adrenals, and ureters in one dense thick mass. Recently we have observed Hodgkin's disease in and about the female urethra. Last year 3 large, polypoid tumors arising from the vaginal wall, and very radiosensitive, proved however, to be the first evidence of a rapidly fatal myeloblastic leukemia.

Following such a complete remission of acute leukemia in a young boy that for a short time we trusted we had been dealing with a leukemoid reaction to infection, the first evidence of return of activity of leukemia was a bilateral hard testicular enlargement to four times normal size.

Priapism is mentioned in all the books as a complication of leukemia, but actually is of rare occurrence.

Whether a young woman having one of these diseases should marry is a question that arises several times a year. This is a delicate matter, since as a rule the patient herself is purposely kept ignorant of the prognosis and if possible even of the name of the disease, although some responsible member of the family is kept informed. With the patient's permission, the fiancé is told all about the disease, and instructed to see to it that the patient does not become pregnant.

If, when the young woman patient is first seen, pregnancy has already occurred, we do not in general advise a therapeutic abortion—certainly not if the pregnancy has gone beyond four months. If pregnancy is earlier than three months, decision about therapeutic abortion should be made on the basis of individual circumstances. In Hodgkin's

TABLE II—PULMONARY PARENCHYMAL LESIONS OF LYMPHOMAS AND LEUKEMIAS

	Roentgen findings per cent	*Autopsy findings per cent*
Hodgkin's disease	38.5	47.0
Lymphosarcoma	29.6	24.5
Lymphatic leukemia	26.5	19.0
Myelogenous leukemia	7.6	13.0

ALL INTRATHORACIC LESIONS OF LYMPHOMAS AND LEUKEMIAS

	Roentgen findings per cent	*Autopsy findings per cent*
Hodgkin's disease	75	88
Lymphosarcoma	54	73
Lymphatic leukemia	72	84
Myelogenous leukemia	18	48

disease there seems some reason to believe that the termination of pregnancy, spontaneously or artificially, at full term or prematurely, gives a stimulus to the disease. However, this impression may have been caused by the added growth of the disease that perforce has been allowed to take place in some cases during pregnancy because the existence of the pregnancy led to withholding treatment of lesions that otherwise would have been treated and kept more or less under control.

One is naturally reluctant to use irradiation about the abdomen or pelvis of a pregnant woman, for fear of injury to the fetus. For the treatment of leukemia in a pregnant woman Forkner has suggested that arsenic be used, rather than irradiation.

Respiratory tract: Any part of the respiratory tract may be affected by any of the lymphomas or leukemias. Mediastinal and hilar lymph node enlargement is so common, except in myelogenous leukemia, that it need not be discussed. It may be noted that in a survey of chest films in 52 cases of myelogenous leukemia, no mediastinal tumors were found, and discrete hilar nodes were noted in less than 10 per cent. However, in a series of 23 autopsies of cases of myelogenous leukemia, myeloidi-

zation of enlarged mediastinal or hilar nodes was found in 47 per cent.

Considering the more obscure and less often thought of lesions of lung parenchyma, a considerable discrepancy may be noted between roentgenographic findings and autopsy findings. This discrepancy naturally is explainable in part by the terminal advance of pulmonary lesions which were not visible when the patient's last chest films were made. Nevertheless, the discrepancy is large enough to suggest that lesions were often missed because chest films were not taken at appropriate times. (See Table II.)

It is perhaps not well enough known that cavitation can occur in Hodgkin's disease of the lung. Not only may abscesses form distal to bronchial obstruction by Hodgkin's disease, or secondary to such rare developments as tracheo-esophageal fistulae, but central break-down can occur in either large or small Hodgkin's nodules in the lungs and produce cavitation with or without the influence of infection or irradiation.

The intrathoracic lesions as found at autopsy have been classified, following Versé, as follows: Mediastinal node lesions, hilar node lesions, mediastino-bronchial node lesions with direct invasion of the lung, mediastino-bronchial node lesions with peribronchial and intrabronchial spread, more or less lobar (diffuse) infiltration of the lung with varying degrees of involvement of the broncho-mediastinal nodes, confluent lobular (isolated circumscribed) focal formations with involvement in various degrees of the broncho-mediastinal nodes, miliary (lympho-hematogenous) foci with involvement in varying degree of the broncho-mediastinal nodes, parietal pleural nodules, and pleural effusion.

It is of interest to note that occasionally in Hodgkin's disease, the intrabronchial mode of spread may include an organization of endobronchial exudate into specific Hodgkin's granulomatous tissue.

Lesions in the chest wall may arise either as rib lesions growing both internally and externally, or they may arise as pleural nodules growing out through the chest wall, to involve ribs, muscle, and subcutaneous tissue.

The intrathoracic lesions, particularly those of the tracheobronchial nodes and central lung parenchyma may be silent for months, even though of considerable bulk, and readily detected roentgenographically, yet they, like other visceral lesions, may be prognostically much more serious than the external nodes to which a disproportionate amount of attention may be paid.

The lesions of the lung and pleura may not respond as well to x-ray therapy as do superficial nodes or even mediastinal nodes. It seems likely that the character of the tissue bed in the lung or pleura accounts for this tendency to show a less favorable response. However, in many instances the regression after irradiation is gratifyingly rapid and seemingly complete.

When a pleural effusion occurs on one side it appears preferable to try first the effect of irradiation, rather than to resort to thoracentesis immediately. In many cases, the effusion will absorb rapidly following irradiation, whereas following thoracentesis, usually the fluid re-accumulates rapidly, and in these cases there seems to be particularly a tendency to multiloculation of the fluid following thoracentesis.

The skeletal system: While marrow infiltration becomes universal in leukemia, and is common in Hodgkin's disease and lymphosarcoma, especially in the later phases, it is when cortical bone becomes affected that the patient is particularly liable to develop severe pain or disability, demanding relief. Figures of the incidence of gross bone lesions affecting cortex have varied widely, and are probably all too low. In Hodgkin's disease reports in the literature of bone lesions found by roentgen examination run around 16 to 20 per cent. It is my own belief that 50 per cent would be nearer the truth, if such lesions were regularly searched for.

The most common type of cortical bone lesion found in Hodgkin's disease is a mixture of osteolytic and osteoplastic change, occurring in half of those cases in which bone lesions are found. The second most common type, representing about 2/7 of the cases with bone lesions, is a purely osteolytic change; and the least common type, comprising about 1/7, is a purely osteoplastic change.

In lymphosarcoma the mixed type, showing both destruction and production of bone, makes up only 1/10 of the cases with gross bone lesions, while the purely osteolytic type accounts for 85 per cent, and the osteoplastic type only 5 per cent.

Thus, contrasting lymphosarcoma with Hodgkin's disease, if a gross bone lesion develops it is three times as likely to be purely destructive in the case of lymphosarcoma as in the case of Hodgkin's disease, and only about one third as likely to be of the purely productive type.

Extensive bone changes in the skull, or in the vertebral column, even with fracture and collapse of vertebrae, may be accompanied by

no other neurological affection than pain.

Prompt relief of pain and in some cases complete or nearly complete restoration of normal roentgenographic appearance of the diseased bone may result from early treatment of these lesions by irradiation, before any deformity has occurred.

The early recognition and treatment by irradiation of the bone lesions complicating lymphomas and leukemias constitute an important part of the improved palliative management of these diseases.

The bone lesions, especially those with extensive osteoplastic changes, may produce an elevation of serum alkaline phosphatase levels. However, the determination of alkaline phosphatase is no longer regarded as of much significance in this field, because so often the patient with bone lesions has impaired liver function, which likewise is reflected in an elevated phosphatase level.

Nervous system lesions of the lymphomas and leukemias constitute a large chapter in themselves. Any of the special sense organs and any part of the central or peripheral nerve system may be directly or indirectly affected by any of these diseases.

Some of the more common or more serious manifestations of neurological lesions deserve brief mention.

Paraplegia may develop fairly rapidly unaccompanied by any detectable gross lesion of the spinal column. If x-ray therapy is given accurately and promptly over the appropriate level in adequate doses, paralysis may disappear more or less completely. For example, a woman with Hodgkin's disease who had complete paraplegia in the summer of 1939 was able to walk in a few weeks and after a few months all signs disappeared except moderate exaggerattion of knee jerks and for years she has walked and climbed stairs normally.

Herpes zoster may be extensive and painful, and may produce large necrotizing lesions that leave many deep scars. Some relief may be afforded by prompt x-ray treatment of the appropriate level of the spinal cord.

Sixth nerve paralysis seems fairly common, as does a partial fifth nerve affection producing anesthesia about the chin.

Horner's syndrome is often seen accompanying enlarged nodes at the base of the neck anteriorly.

Lenk has stated that it is so unusual for Hodgkin's nodes to cause phrenic nerve paralysis that the discovery of such paralysis speaks against

a diagnosis of Hodgkin's disease. However, either phrenic or recurrent laryngeal paralysis may occur in any of the lymphomas or leukemias, being seen particularly with Hodgkin's disease and lymphosarcoma.

Pruritus, so common in Hodgkin's disease (about 30 per cent), and not infrequently seen in other lymphomas and in lymphatic leukemia, while usually more or less general, may in some cases be regionally distributed in such a way as to suggest a neurological basis. Itching should always be regarded as a sign of the presence of active disease.

In one case of Hodgkin's disease a completely intractable and severe peripheral neuritis made the patient's last year of life miserable.

Retinal hemorrhage may be the first clue to an acute trend in a leukemic patient.

The apparently benign orbital lymphoma may be followed in a few years by generalized lymphosarcoma.

Jaundice develops from various causes in many patients with lymphomatous or leukemic disease. It is often well nigh impossible to know how much to blame, respectively, hepatitis, which may be of the homologous serum variety in those who have received transfusions, or portal obstruction, or hemolysis, as the factor responsible for the jaundice, since the usual tests may fail to give a clear answer, and there is often reason to believe that all possible factors or some combination of them is responsible.

Ascites and marked edema of the lower extremities are very likely to occur in the patient who not only has ample reason for these phenomena on the basis of obstruction by enlarged nodes, but also has marked hypoproteinemia.

Anemias of various kinds are encountered in these diseases. Although some may be relieved by iron, by improvement in diet, by liver or transfusions, yet many, apparently caused mainly by irreversible marrow impoverishment, persist despite all measures. Although we have used transfusions much more in recent years, it is not clear that a great deal more has been accomplished thereby, and certainly it is true that one runs into a high incidence of both immediate transfusion reactions and hemolytic states, that tend to cast some doubt on the efficacy of transfusions if used on a large scale for these diseases. Not at all uncommon is it to find that a patient with leukemia has a lower red cell count following transfusion.

The hemorrhagic diathesis is particularly troublesome in leukemia,

especially in the acute cases, and in the acute exacerbations of the chronic cases, but may occur in any of the other diseases under consideration. It is usually, but by no means always, accompanied by a reduced platelet count, and in many cases the platelet count may be below 50,000, and yet no evidence of bleeding tendency will be found. It seems most likely that the bleeding is more often dependent on damage to integrity of vessel walls than any other factor. There is no single satisfactory method of overcoming the bleeding tendency, and in most cases the use of vitamin K, or C, thromboplastin, fibrin foam, calcium, or Koagamin is ineffective. The value of rutin remains to be tested.

Hypoproteinemia is often a serious problem in the more advanced cases, and in many of these is most refractory to treatment. It often is partly responsible for edema in a patient whose abdomen is so full of lymphomatous disease that pressure is also partly responsible for the edema. Such a patient may be unable to eat, and unable to respond to transfusions of blood or plasma or infusions of casein hydrolysates.

The basal metabolic rate may be considerably elevated, not only in leukemia but in Hodgkin's disease and lymphosarcoma, especially in the more active cases. Some years ago, attempts were made to treat leukemia by thyroidectomy, but one hears no more about that today. Because of the effect of thiouracil in lowering the basal metabolic rate in hyperthyroidism and in occasionally causing granulocytopenia, it seemed reasonable to try its effect on leukemia, but no consistent beneficial effect was found.

About 20 years ago a rather dogmatic statement appeared in the literature to the effect that the level of the basal metabolic rate was the best indication for the treament of leukemia, and that if the basal metabolic rate were high, the case could be safely treated, even though the white cell count were low. This statement seemed a rather dangerous one then, and although it has recently been reiterated, it still seems preferable to advise a broader perspective in treating leukemia than to depend on any such single sign. One can think of various situations, such as cases in a near terminal stage, cases of myeloid leukosarcoma, cases of myeloid leukemia with extensive lymph node myeloidization, always a bad prognostic sign, or those with pronounced bleeding tendency in which, although the basal metabolic rate would be markedly elevated, other factors would indicate great caution in radiation therapy or would

even indicate withholding it entirely.

Fever has been taken for granted as a common feature of lymphomatous or leukemic disease on the assumption that the disease itself directly causes the fever. The true Pel-Ebstein cycle of regularly recurring febrile and afebrile periods is a striking phenomenon when seen in Hodgkin's disease, but actually is not very common. Practically every patient with Hodgkin's disease, lymphosarcoma or leukemia has bouts of fever at some time during the course, but as a general rule, the fever follows no distinct pattern. Considering the frequency with which intercurrent or terminal infections occur, the occasional marked response to sulfonamide or penicillin therapy, and the known impairment of the reticuloendothelial system in these diseases, it is a matter for speculation whether the fever is actually directly due to the lymphomatous or leukemic process, or whether it may not indicate lowered resistance to invasion by bacteria or their toxins.

Diagnosis is notoriously difficult in lymphomas and leukemias. While there are many clean cut cases, about which there is no diagnostic uncertainty, yet there are many others about which even the most skilled tumor pathologists will disagree. The possibility that Hodgkin's disease and lymphosarcoma may clinically simulate or be simulated by other diseases, makes it particularly necessary to obtain proof of diagnosis histologically, if at all possible.

Lymphosarcoma has been simulated by neuroblastoma, cancer of the pancreas, liposarcoma, and various other widely dissimilar tumor processes. It is often difficult to differentiate clinically between bronchogenic carcinoma and Hodgkin's disease. Tuberculosis or Boeck's sarcoid may exactly simulate Hodgkin's disease, and vice versa.

Even leukemia may be masked at first. It is often difficult to say where refractory anemia leaves off and leukemia begins. Recall that malignant tumors metastatic to bone may cause the appearance of some immature blood cells in the peripheral blood. Enlarged lymph nodes in a patient with a leukemic blood picture may show carcinoma rather than leukemia. Too, the presence of both leukemia and cancer, or of a lymphoma and cancer, in the same patient is not so rare. It is a good general rule, that whenever a patient with chronic leukemia or lymphoma does not respond to treatment as well as was expected, one should look particularly for some obscure cancer.

The diagnosis of leukemia may in most cases be fairly well estab-

lished by examination of the peripheral blood alone, but it is usually advisable to examine as well thin smears of 0.1 or 0.2 cc. of sternal marrow obtained by puncture. Sternal puncture may be of decisive value in many doubtful or clinically borderline cases. Yet in the interpretation of the marrow obtained by the puncture method, one must always keep in mind that to a greater or less extent there is an admixture of circulating blood. Thus in the cases with a node biopsy showing lymphosarcoma and a blood count suggestive of lymphatic leukemia, say 25,000 white cells with 75 per cent small lymphocytes, the finding of about 50 per cent lymphocytes in the marrow smears has to be somewhat discounted because, obviously, so many of the lymphocytes are there because of the admixture of circulating blood. Occasionally it is preferable to obtain a surgical biopsy of the marrow.

If any accessible enlarged nodes are found it is usually advisable, in order further to round out the diagnosis, to do a biopsy of the node.

The following example illustrates the value of having, wherever possible, a check on the diagnosis in these three ways, lymph node, peripheral blood, and sternal marrow. A patient with a general lymph node enlargement came in with a node biopsy that was interpreted at first as lymphosarcoma. Then it was noted that the blood smears showed some immature myeloid cells, whereupon a marrow puncture was done, and showed myeloblastic leukemia. With this information, reëxamination of the node disclosed that the cells that resembled lymphosarcoma cells were of myeloid origin. The practical importance of this differentiation lay in the ability to know thus early that we were dealing with an aggressive case of myeloblastic leukemia with extremely bad prognosis and practically a contraindication for vigorous x-ray treatment, rather than with a case of lymphosarcoma, in which x-ray treatment might have offered a good prognosis for temporary control of the disease.

In lymphosarcoma and Hodgkin's disease the diagnosis must be based, if possible, on biopsy of a representative node. Too often, for cosmetic reasons, a small outlying node is selected that fails to yield a satisfactory specimen. With experience one learns to be able to select whichever small peripheral and easily accessible nodes are likely to be significant, judging them by their change to globular or nodular shape and firm to hard consistency, but without such experience, it is better to select, if possible, a node which has been enlarged longer, and is part of a group of nodes, so that it seems likely to be more certain of

being representative of the disease process one is trying to identify.

In general, a formal surgical biopsy is to be preferred. Sometimes there is only one large fused mass of nodes with no single node available for dissection. In such cases a wedge may be removed. It is better practice in such a case to retract the skin so that the incision in the skin will not overlie the incision in the capsule of the tumor. There will then be less danger of fungation of the tumor through the wound.

Many cases of lymphomatous disease are seen in which there is no peripheral node available for surgical biopsy. The patient may have only one small node behind the inner end of the left clavicle at the junction of the thoracic duct with the subclavian vein—the signal node. He may have only a mass projecting from one side of the mediastinum. He may have only an enlarged firm spleen. In such cases an aspiration biopsy may yield a specimen that is quite satisfactory to a pathologist who has been willing to make himself competent in the interpretation of such material.

In a review of biopsies in 242 cases of proved Hodgkin's disease, aspiration biopsy was selected as the first method to try in twenty-five cases, and was diagnostically successful in fourteen cases, or 56 per cent. In the eleven unsuccessful cases the aspiration biopsy failed to yield sufficient or satisfactory material, and it was necessary to resort to a surgical excision. Even in most of the failures enough information was gained to suggest a lymphomatous process, and in some cases such reports as lymphoid tissue, or a question as between Hodgkin's disease and tuberculosis gave a lead pointing away from a previously considered diagnosis of carcinoma. As showing the value of biopsy by such a simple method in the differential diagnosis of clinically difficult cases, it is of interest to note the provisional diagnoses that had been made in a small series of nine cases in which aspiration biopsy proved the presence of Hodgkin's disease; namely, Hodgkin's disease in only one case, unspecified lymphoma in three, lymphosarcoma in one, tuberculous lymphadenitis in one, metastatic carcinoma in two, and carcinoma of thyroid in one. A successful aspiration biopsy diagnosis in fourteen of twenty-five attempts is not bad for this group of diseases, when one recalls that 10 years ago, when aspiration biopsy was already firmly established as an indispensable diagnostic method for many malignant tumors, a pathologist particularly experienced in this field would not attempt to diagnose Hodgkin's disease or lymphosarcoma on aspirated material.

The dangers of aspiration biopsy of the lung and spleen have been grossly exaggerated, although certainly they are not procedures to be undertaken lightly by the inexperienced. In the reported fourteen successful aspiration biopsies of Hodgkin's disease, three were obtained by puncture of the lung, and one was from the spleen. These were all cases in which, at the time the procedure was chosen, there was no other way of obtaining histological proof.

Treatment. Articles in the lay press about some of the newer forms of therapy suggest to the layman that the cure of lymphomatous and leukemic diseases is just around the corner, and in fact, many laymen have gained the erroneous notion that it should be possible now to effect a cure by these methods, and that all that is necessary is to find the specialist who has access to these new agents.

Particularly in the limelight at present are the radioactive isotopes, and the nitrogen mustards. It does seem certain that internal whole body irradiation, afforded by radioactive isotopes, and chemotherapy, probably with more effective compounds than the currently available nitrogen mustards, are methods of treatment that are here to stay. Both the radioactive isotopes and the nitrogen mustards have been shown to be useful tools, but neither method has as yet equalled the all around efficacy of roentgen therapy, when one considers all the different ways in which roentgen therapy can be used. Each has a certain field of usefulness now, and each can be regarded as a pioneer method, with the possibility that considerably greater effectiveness will be brought about by improvements. Clinical trial of nitrogen mustards was suggested because of the observations made by the Chemical Warfare Service that these agents produced a marked leukopenia, caused apparently by a selective destructive action on lymphatic tissue and bone marrow, and that this action on cells resembled that of roentgen rays. Clinical experience has shown that HN_2 (di-beta-chloroethyl amine) and HN_3 (tri-beta-chloroethyl amine) are useful chiefly in those cases of Hodgkin's disease in which generalization has begun, and constitutional symptoms are present. They are too toxic and too ineffective for use in the ordinary relatively early and regional case, in which x-ray therapy can bring about as a rule marked remission with relatively little toxic side-effect. To a less extent are the nitrogen mustards useful in very advanced cases of Hodgkin's disease that have become refractory to x-ray treatment, or in lymphosarcoma, lympholeukosarcoma, and

chronic lymphatic leukemia. They are of little or no use in myeloid leukemia, in any of the acute leukemias, or in the more aggressive forms of lymphosarcoma.

The radioactive isotopes that have been used for lymphomas and leukemias are chiefly radiophosphorus, and radiosodium, and recently radiomanganese. Our experience with radioactive isotopes in connection with this group of diseases has been entirely with radiophosphorus. Its chief field of usefulness is, in the order named, in polycythemia vera, chronic myelogenous leukemia, and chronic lymphatic leukemia. It has the advantage of causing no radiation sickness. Its great disadvantage is that it is not sufficiently selective, and its destructive effect on marrow is its limiting factor when large and repeated doses are employed. It does not in general treat lymphosarcoma satisfactorily, and almost uniformly its results in Hodgkin's disease have been disappointing. For all the acute leukemias radiophosphorus is hazardous, as is any other form of total body irradiation.

Neither the nitrogen mustards nor radiophosphorus can supplant roentgen therapy, and they are best regarded, not as competitive agents, but as complementary tools. The treatment of leukemia can seldom be exclusively carried out throughout the course by means of radiophosphorus. In most cases situations arise demanding x-ray therapy either as a supplement, or alone. It is most certain that nitrogen mustards could not alone control Hodgkin's disease. Their best use appears to be as a supplement to x-ray therapy. The usual early case with localized disease can be much better treated by local x-rays, and the same is in general true of the cases in an early stage of generalization, in which the disease is still relatively regional. When constitutional symptoms, such as fever and night sweats appear, then, provided the white cell count is reasonably good, nitrogen mustard may be an effective palliative agent, producing remissions lasting from two or three weeks to sometimes seven or eight months.

Another chemotherapeutic agent, urethane, was announced in *Lancet* last May, as effective in the palliation of leukemia. It was said to be effective in lowering the white cell count, to have more marked effect on the more immature white cells, and to reduce the size of the spleen. It was promptly tried in this country following publication by the English workers, but its effects have been disappointing. We have been unable to confirm any more marked effect on the less mature cells.

External irradiation, considering all its possible various forms, remains the most generally useful method of treatment of all the lymphomas and leukemias. This can still be said, while taking into account the many cases in which results are not satisfactory. The acute leukemias, for example, seldom derive any great benefit from radiation. Its use in acute leukemias may be totally contraindicated, or restricted to minor palliative measures, such as relief of pain caused by leukemic changes in bone, or relief of a complicating local infection of the skin, where the combination of infection and leukemic infiltration causes resistance to usual methods of treating infection, and where only treatment by a small dose of x-rays may cause the inflammation to subside.

Whereas lymphosarcoma used to be held up as the classical example of radiosensitivity, experience has shown that some cases may be rather radioresistant, and, moreover, there are certain very acute cases of lymphosarcoma that are so rapidly growing, and so complicated by fever, signs of infection and bleeding tendencies that they respond about as poorly as cases of acute leukemia.

On the other hand, there are certain very chronic, low-grade lymphomas and leukemias in which the question arises as to whether they should be treated at all, particularly since statistically it is difficult to produce evidence indicating any great prolongation of survival time as a result of irradiation. Especially in those chronic forms of leukemia in which the patient looks and feels well, or nearly well, does it seem doubtful that treatment should be advised.

Nevertheless, the great bulk of cases of Hodgkin's disease, lymphosarcoma and chronic leukemia have symptoms that are incapacitating, and need relief, and by and large irradiation in some form is the one agent that can best bring about that relief. Despite the failure of statistics to show any marked increase in survival time following irradiation, any one who has treated such diseases for many years could cite numerous specific cases in which there could be no doubt that irradiation had prolonged life for many years.

The range of ways in which roentgen therapy can be applied is indeed wide. Beginning with low voltage apparatus at 50,000 volts for treatment of superficial lesions, we can ascend the scale of voltage and penetration, through ordinary high voltage apparatus (180,000 to 250,000 volts), to the million volt machines useful for some bulky deep lesions, because it is a peculiar property of the supervoltage rays that

while delivering greater depth doses, they cause much less constitutional disturbance and much less skin reaction. Treatment with x-rays can be accurately applied to a circular field as little as 1 cm. in diameter, to an irregular area, or to very large fields. The whole torso or the whole body can be sprayed intermittently, or the whole body can be continuously treated for days or even weeks at very low intensity in the Heublein unit, where the patient receives irradiation in his bed day and night.

The Heublein method of external whole body low intensity prolonged irradiation by x-rays seems to add to the survival period and to the periods of remission in Hodgkin's disease, lymphosarcoma, and chronic lymphatic leukemia. Since 1940 interest in the internal, somewhat selective method of whole body irradiation afforded by radiophosphorus has tended to shunt cases away from the Heublein method, for which, however, there is still a place.

The results in Hodgkin's disease, lymphosarcoma, lymphatic leukemia and myelogenous leukemia have recently been surveyed for the 11 year period, 1930 through 1940, in terms of the 5 year survival curves. These figures reflect almost exclusively the results of therapy by means of external irradiation and general supportive measures, since our work with radiophosphorus did not begin until February 1940, and at that time no chemotherapeutic method was in vogue, except for the occasional use of arsenic for leukemia in moderate doses.

For the most part the net 5 year survival figures show an improvement over our previously reported results.

Hodgkin's disease shows 20.5 per cent 5 year survivals of 283 patients, as compared with 17.7 per cent for 265 cases from 1918 through 1935.

Lymphosarcoma shows 26.3 per cent of 308 patients surviving 5 years, as compared with 15.9 per cent of 132 cases for the years 1918 through 1933.

Lymphatic leukemia shows 15.7 per cent 5 year survivals of 125 patients as compared with 9 per cent reported for 77 cases from 1917 to July 1, 1929.

Myelogenous leukemia* shows 5.3 per cent 5 year survivals of 57 patients, as compared with 5.9 per cent reported for 68 cases from 1917

* The figures for leukemia, however, are not strictly comparable, since the later figures excluded very acute cases, and the earlier figures excluded only those lost to follow-up within 6 weeks.

through July 1, 1929.

Thus, there has been a decided improvement in the 5 year survival figures for Hodgkin's disease, lymphosarcoma, and lymphatic leukemia, while the figure remains unimproved for myelogenous leukemia. Just why there has been a failure to secure improved results in myelogenous leukemia is a matter for speculation. Possibly a greater proportion of the accepted cases has been of a somewhat more acute variety. Then, too, in myelogenous leukemia, as far as radiation therapy is concerned, it is usually a matter of irradiation of spleen, sometimes of long bones, or of the entire body. Whenever in a case of myeloid leukemia skin nodules, or enlarged nodes, or a leukemic tumor appears, the case is pretty certain to have from then on a more acute trend, and the tendency is to be much more conservative with radiation. On the other hand, chronic lymphatic leukemia, lymphosarcoma, and Hodgkin's disease are more nearly alike in that they lend themselves better to the treatment of lesions anywhere in the body, and the discovery of a skin infiltrate, a destructive bone lesion, or a tumor in some atypical location is simply an indication for more treatment, rather than necessarily an index of acute trend and probable uselessness of further irradiation. Perhaps we should be more aggressive in attempting treatment of the more aggressive forms of myeloid leukemia.

In conclusion, it may be emphasized that leukemias and lymphomas are important because of their not inconsiderable mortality and morbidity, especially among the younger elements of the population, because their range of morbidity brings them within the scope of every kind of practitioner, and because they are increasingly valuable to the investigation of the cancer problem.

They may now be more hopefully regarded, because as methods of diagnosis and treatment have approached greater precision we begin to detect promises of curability in certain types of Hodgkin's disease and lymphosarcoma, and appear to have demonstrated greater palliative and life prolonging effectiveness of therapeutic methods for most of the members of this heterogeneous family of diseases.

TUMORS OF THE STOMACH*†

ARTHUR PURDY STOUT

THE stomach is a neuro-muscular pouch provided with a powerful sphincter muscle at the pylorus where it joins the duodenum. In the proximal two-thirds, called the fundus, it is lined by a complex mucous membrane which is provided with a large number of highly specialized cells which secrete the acid and ferments of the gastric juice. These are surmounted by a thin layer of short pits or tubes from the cells of which a protective layer of mucus is produced. In the distal third of the stomach called the antrum and pylorus the gastric pits are much lengthened and the specialized cells correspondingly reduced so that here, where the food is made ready for propulsion through the pyloric sphincter, much mucus and little gastric juice is secreted. The mucosa and its vascular submucosa are loosely attached to the muscular walls and are thrown up into folds or rugae provided with a slender muscle of their own. The stomach is furnished with many blood vessels and lymphatics and a rich and complex nervous mechanism connected with the vagus and splanchnic nerves so that its activities are profoundly influenced by the activities of the organism as a whole.

The tumors which develop in the stomach are derived from the cells of the tissues which compose it. The vast majority of them are malignant and develop from the mucous cells. Attention will be focussed upon these and the rest must be dismissed with a word or two. The commonest benign tumors are the adenomatous polyps composed of mucous glands. These sometimes give symptoms but the most important fact about them is that they may become malignant. But polyps are rare in comparison with carcinomas. Tumors, most of which are benign, spring from the smooth muscle forming nodules which project both within and outside of the stomach. It is well to remember that when such tumors ulcerate they sometimes give rise to massive hemorrhages. The submucosal lymphoid tissue also gives rise to malignant tumors called

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lymphosarcomas. These grow in very much the same fashion as do carcinomas, produce comparable symptoms and are generally treated in the same way except that, since they are somewhat radiosensitive, radiotherapy is ordinarily used after their removal. There are other uncommon benign tumors of fat, connective tissue, blood and lymphatic vessels, nerve sheaths and from congenitally misplaced epithelial structures in the stomach wall.

Beginning sometimes as early as the third decade of life, processes of inflammation and atrophy commence to appear in the distal third of the stomach and may extend to the fundus. These can be divided into (A) irritational phenomena consisting of inflammatory cell infiltrations both diffuse and in the form of lymph follicles, edema and vascular engorgement; and (B) glandular changes which consist especially of a transformation of gastric glands into those of the intestinal type, patchy replacement of fundus glands by those of the antral type and microcystic dilatation of the mucous glands. These changes are seldom found to any marked degree in the fundus but tend to grow progressively more marked in the distal part of the stomach with the advance of years. The changes sometimes result in thickening and sometimes in thinning of the gastric mucosa. Although the purely inflammatory exudative features of chronic gastritis probably have a direct relationship with the formation of peptic ulcers as Collins[1] has pointed out, it is doubtful if they have any importance in cancer formation. The glandular changes, on the other hand, may be precancerous for they are apt to be marked in cases of stomach cancer. But rarely, if ever, is it possible to trace a microscopic relationship between the two as Guiss and Stewart[2] have pointed out and so it remains uncertain whether or not these atrophic changes are definitely precancerous (Stout[3]). It must also be stressed that carcinoma of the stomach not only develops in just those parts of the stomach where the most marked changes of gastritis are commonly observed, namely along the lesser curvature or adjacent to it in the antrum and pylorus, but it also develops in the fundus and at the cardia where they are very uncommon. Whatever one believes about atrophic gastritis, it is certain that in pernicious anemia in which atrophy of the gastric mucosa occurs to a marked degree, there is a much higher gastric cancer rate than in a comparable age group of the general population; 40 or more times as great according to Rigler and his coworkers.[4] There can be no question about the fact that atrophic gastritis is present and

often to a marked degree in all but about 6 per cent of stomachs with gastric cancer (Stout[3]). There is good reason to believe that adenomatous polyps are precancerous growths but again the relationship between hypertrophic gastritis and gastric cancer is less certain. Other factors have been suggested as precancerous lesions. Ewing[5] mentions congenitally misplaced epithelium in the gastric wall, avitaminosis, and chemical and bacterial toxins, and several authors including Rigler[4] and Ehrmann[6] have suggested that hereditary predisposition exercises some influence in the development of gastric cancer but none of these statements has been proved. Whether or not carcinoma may develop from a preëxisting peptic ulcer remains a hotly debated question and the arguments pro and con will not here be rehearsed but there is no doubt about the fact that it is impossible always to distinguish between simple and cancerous ulcers of the stomach by any of the clinical diagnostic methods at our command and the diagnosis can only be reached in some after microscopic study of stained sections. This is a fact of major importance in the treatment of gastric lesions (Allen[7]). In summary it must be admitted that little is known about the etiology of gastric cancer (Ivy[8]).

Carcinoma of the stomach is a neoplasm which is slightly more common in males, it is rarely seen before the beginning of the fifth decade of life, it may develop in any part of the stomach but is commonest in the cephalad half of the distal third. The histological variations of gastric carcinoma are of such slight importance that here they will be ignored. It is, however, of value to know how cancer grows in the stomach and its effect upon gastric morphology and physiology, for diagnosis depends upon the changes produced by it. Carcinoma should be envisaged as originating from a focal point or a group of foci in the mucosa or possibly occasionally from heterotopic epithelial cells in the gastric wall. It tends to grow in all directions, into the lumen, penetrating through the gastric wall and along the gastric wall paralleling its surface. But the rate of growth in one or another direction differs greatly in different cases and this gives rise to the different gross forms observed. If growth is chiefly into the lumen, a fungating tumor results which may sometimes become secondarily excavated by superficial ulceration. If growth is chiefly away from the lumen, penetrating the gastric wall, ulceration occurs almost at once and a shallow bowl-shaped ulcer with little or no elevation of its margins is formed. This is a common cancer type and is responsible for most of the difficulties of differ-

ential diagnosis between benign and malignant ulcers. In a third variety called variously carcinoma in situ (Mallory[9]), slowly progressive muco-erosive cancer (Gutmann et al[10]) or superficial spreading cancer (Stout[11]), the tumor spreads centrifugally in the mucosa and submucosa over a relatively wide area before penetrating deeper into the gastric wall. It usually produces a shallow bowl-shaped ulcer limited to the mucosa and submucosa. There is another much rarer variety of gastric cancer in which there is deep centrifugal spread throughout the stomach wall, thickening and stiffening it but leaving the mucosa uninvolved. This is called linitis plastica or leather bottle stomach. Any one of these varieties of carcinoma may be associated with a chronic peptic ulcer of benign aspect either in the cancer area or in some other part of the stomach. In the last two hundred carcinomas of the stomach resected at the Presbyterian Hospital, 65 were too extensive to permit grouping. The remaining 135 were grouped as follows: penetrating with ulceration 40 per cent; fungating 37 per cent; superficial spreading 20 per cent; linitis plastica 3 per cent. Of the 200, 16 or 8 per cent were associated directly or indirectly with peptic ulcers.

The cancerous growth, no matter what its type, generally interferes with gastric motility over a greater area than is the case with simple peptic ulcer. This is partly because of the scar tissue which accompanies its growth but by no means altogether and it must be confessed that the real reason is unknown. It is also true that in the majority of cases there is a reduction in the secretory activity of the gastric glands which may become achylia; but the reduction does not always occur and there may be actual hyperacidity. Obstruction of the pylorus or cardia because of mechanical blocking by the tumor, muscular hypertrophy or spasm, is a variable factor but generally does not dominate the picture in early neoplasms.

Metastasis from gastric carcinoma is generally early going first to the nodes along the greater and lesser curvatures and later to the liver, lungs and to other lymphatic stations. When it progresses locally outside of the stomach, it invades adjacent organs and structures such as the pancreas, liver, transverse colon, and the mesenteries, omentum and retroperitoneal tissues. It respects the duodenum but not the esophagus and diaphragm. Widespread metastases are not very common.

The only symptoms and signs which will be stressed at this time are the early ones when it may still be possible to cure the patient.

There are two characteristic modes of onset in gastric cancer: (A) After a lifetime of good health a man or woman suddenly begins to suffer from "indigestion consisting usually of epigastric pain or discomfort or a feeling that food is remaining too long in the stomach" (Alvarez;[12] Harris[13]). This may be accompanied by loss of appetite, weight and strength (McVicar and Daly; [14] Spriggs[15]). (B) In a second group the patients have suffered for years with gastric disorders which may be due either to gastritis or peptic ulcer (Usland;[16] Allen;[7] Palmer[17]). Suddenly the character of the symptoms changes and the patient starts to go downhill. Vomiting, pain, occult or obvious bleeding, flatulence and a palpable mass are all late signs which often only appear after the cancer is hopelessly advanced.

Diagnosis is exceedingly difficult in the early stages. The majority of writers feel that examination by x-ray is the most reliable method but even this may fail to detect a very early lesion or differentiate with assurance between a peptic ulcer and an ulcerated cancer. By this method derangements of motility, pyloric obstruction, projecting tumors, ulcerating lesions and changes in the rugae can all be visualized and their significance interpreted with a high degree of accuracy by an experienced radiologist. The reflected images of these same changes can be seen by the gastroscopist although not as completely because there are blind spots which cannot be inspected. With care in performing the analysis and obtaining the specimens, Holman[18] believes that examination of the gastric contents is of great value in differentiating between peptic ulcer and cancer. He found that 100 per cent of patients with peptic ulcers had a normal or elevated secretion of hydrochloric acid and 96 per cent of carcinomas of the stomach had a low acidity or anacidity. Lactic acid in the gastric contents strongly suggests the presence of cancer but does not prove it (Davidson and Calder[19]).

All students of the subject, physicians as well as surgeons, are in agreement that the only possible chance of curing gastric cancer is by gastrectomy, while the carcinoma is still confined within the stomach and its immediate removable environs. This means immediate and thorough investigation by x-ray, gastroscopy and chemical analysis of gastric secretions of every individual over forty who complains of a little indigestion which persists without known cause, with frequent repetitions of the examinations, if necessary, and surgical exploration if the symptoms persist and remain unexplained after four weeks treatment.

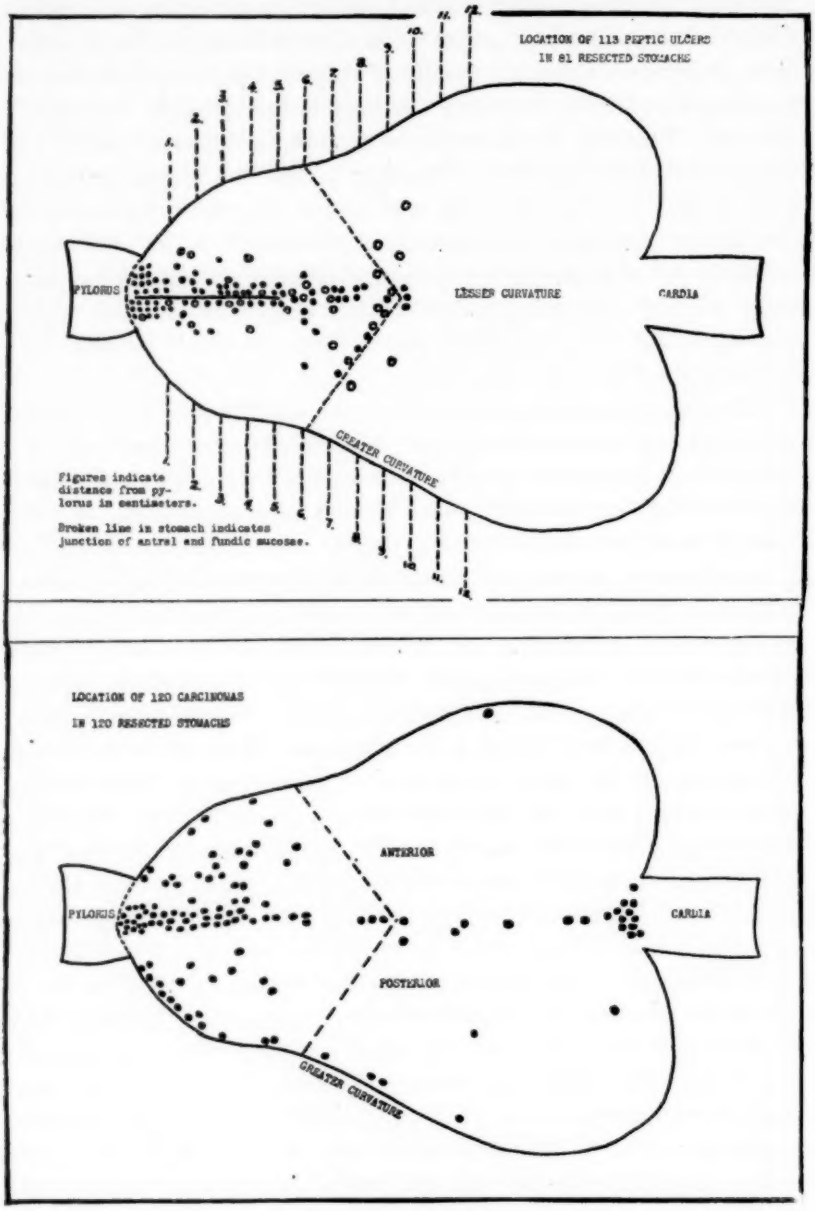

Fig. I

Comparison of the location in the stomach of 115 peptic ulcers and 120 carcinomas. In the diagram the stomach is represented as having been cut open along the greater curvature with the anterior wall above and the pylorus at the left.

It means investigation by the same means of every gastric ulcer which fails to heal progressively and completely after hospitalization and adequate ulcer treatment for four weeks. If with or without an ulcer there is found low acid secretion or achylia, if lactic acid is present, or if there is suspicion of cancer after examination by a competent radiologist and/or gastroscopist, gastric resection should be carried out at once without further delay, for this is good treatment for a simple gastric ulcer and it is the only method by which more early gastric cancers can be cured. Many surgeons consider it mandatory to resect the stomach if an ulcer is over 2 centimeters in diameter because of the relatively high incidence of cancer among large ulcers (Allen[7]). The same advice can be given for all ulcers on the greater curvature and in the fundus because of the extreme rarity of benign peptic ulcers in these situations.

Attempts have been made by St. John, Swenson, and Harvey[20] and by Dailey and Miller[21] to survey large groups of middle-aged and elderly men and women without gastrointestinal symptoms with the hope of discovering and treating unsuspected cancers of the stomach. These show that it is possible to uncover unsuspected gastric neoplasms if individuals are willing to submit themselves to periodic examinations and if experts in diagnosis can be found who are willing to devote a considerable amount of time and effort to the project. Whether or not such examinations can be carried out on a large proportion of the elderly population remains to be seen.

That resection of the stomach is worth while is indicated by the five year cure rate of around 30 per cent of cancerous stomachs removed at the Mayo Clinic (Walters[22]). The fact that about one-third of the cancerous stomachs resected at the Presbyterian Hospital were so far advanced that they could not be typed calls attention to the beneficial effects of gastrectomy as a palliative procedure in incurable cases. The remaining months or years of such patients are rendered much more tolerable by ridding them of a foul gastric tumor; pain vanishes, appetite returns, weight and strength increase until recurrences or metastases finally bring the end.

At the present time according to Oughterson,[23] 58 per cent of gastric cancer patients never reach a hospital and in only about 2 per cent of all gastric cancer cases are five year cures effected. There is little doubt that these figures could be improved if more patients could reach the operating table in a curable condition. To accomplish this physicians

must be eternally vigilant for the slight equivocal evidences of early cancer. It is especially important to regard ulcer of the stomach as a serious disease, needing prompt and careful investigation and medical treatment without any procrastination, followed by surgical resection if progress has been unsatisfactory after the elapse of a month. Perhaps most important of all physicians should realize that if they are unwilling to submit their patients for surgical treatment until the clinical diagnosis of carcinoma is manifest, they are causing these unfortunates to lose their only chance of cure.

REFERENCES

1. Collins, V. P. Peptic ulcer and chronic gastritis, *Ann. Surg.*, 1943, *118*:1005.
2. Guiss, L. W. and Stewart, F. W. Chronic atrophic gastritis and cancer of the stomach, *Arch. Surg.*, 1943, *46*:823.
3. Stout, A. P. Pathology of carcinoma of the stomach, *Arch. Surg.*, 1943, *46*:807; and Gastric mucosal atrophy and carcinoma of the stomach *New York State J. Med.*, 1945, *45*:973.
4. Rigler, L. G., Kaplan, H. S. and Fink, D. L. Pernicious anemia and the early diagnosis of tumors of the stomach, *J.A.M.A.*, 1945, *128*:426.
5. Ewing, J. Etiologic indications of early gastric cancer, *Rev. Gastroenterol.*, 1940, *7*:305.
6. Ehrmann, R. Heredity an important factor for the early diagnosis of gastrointestinal cancer, *Am. J. Digest Dis.*, 1946, *13*:25.
7. Allen, A. W. Gastric ulcer and cancer, *Surgery*, 1945, *17*:750.
8. Ivy, A. C. Gastric physiology in relation to gastric tumor, *J. Nat. Cancer Inst.*, 1945, *5*:313.
9. Mallory, T. B. Carcinoma in situ of the stomach and its bearing on the histogenesis of malignant ulcers, *Arch. Path.*, 1940, *30*:348.
10. Gutmann, R. A. C., Bertrand, I. G. and Péristiany, T. J. *Le cancer de l'estomac au début.* Paris, Doin, 1939.
11. Stout, A. P. Superficial spreading type of carcinoma of the stomach, *Arch. Surg.*, 1942, *44*:651; and *J. Nat. Cancer Inst.*, 1945, *5*:363.
12. Alvarez, W. C. How early do physicans diagnose cancer of the stomach in themselves? *J.A.M.A.*, 1931, *97*:77.
13. Harris, S. Early symptomatology and diagnosis of gastric cancer, *Am. J. Surg.*, 1936, *31*:225.
14. McVicar, C. S. and Daly, J. Diagnosis of operable carcinoma of the stomach, *Ann. Int. Med.*, 1927, *1*:145.
15. Spriggs, E. Early recognition and treatment of cancer of the stomach, *Brit. M. J.*, 1928, *2*:838.
16. Usland, O. Ueber die Bedeutung der chronischen Gastritis für die Entwicklung des Magenkrebses, *Acta Chir. Scandinav.*, 1935, *76*:485.
17. Palmer, W. L. Duration of gastric cancer, *Gastroenterology*, 1943, *1*:723.
18. Holman, C. Diagnosis of gastric carcinoma and peptic ulcer, *J.A.M.A.*, 1937, *108*:1383.
19. Davidson, L. S. P. and Calder, A. Diagnosis of carcinoma of stomach with special reference to lactic acid, *Practitioner*, 1932, *129*:584.
20. St. John, F. B., Swenson, P. C. and Harvey, H. D. An experiment in early diagnosis of gastric carcinoma, *Ann. Surg.*, 1944, *119*:225.
21. Dailey, M. E. and Miller, E. R. Search for symptomless gastric cancer in 500 apparently healthy men of 45 and over, *Gastroenterology*, 1945, *5*:1.
22. Walters, W. Malignant lesions of the stomach, *Arch. Surg.*, 1942, *44*:636. Walters, W., Gray, H. K. and Priestley, J. T. Malignant lesions of the stomach, *J.A.M.A.*, 1941, *117*:1675.
23. Oughterson, A. W. Discussion of paper by Walters, Gray and Priestley, *J.A.M.A.*, 1941, *117*:1680.

THE SURGICAL TREATMENT OF BONE TUMORS*

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FROM earliest times the surgical treatment of bone tumors has been an established and accepted mode of therapy. That it has held its place up to the present time is an admission of failure on the part of the profession to discover a more ideal method since surgery in many instances implies a mutilating operation. When roentgen-rays and radium were first used in these cases it was hoped that perhaps one or both of these agents might prove the answer to the problem and that surgical procedures, such as amputation and resection, might be relegated to the past and become merely of historical interest. That this has not been the case is a distinct disappointment. In most instances, except when dealing with the benign giant cell tumor and a few of the radiosensitive types of malignant tumors of bone, we have found that the dose of radiation that will destroy or at least permanently inactivate the tumor generally produces irreparable damage to the surrounding normal tissues. Therefore it has been necessary not only to persist in the use of surgical methods but to try to expand them. At the same time surgeons have explored the possibility of substituting for amputation the less drastic procedure of radical resection associated with bone transplants. In selected cases these conservative operations have in many instances proven a satisfactory means of extirpating the primary growth and at the same time saving the limb. Phemister of Chicago was a pioneer in developing this type of conservative surgery. We have utilized it for some years and with increasing confidence that it has a definite place in the treatment of certain types of both malignant and benign tumors of bone.

In the brief time allotted it seems best to outline the indications for surgery in some of the more important tumors of bone, first listing them according to an accepted classification.

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Benign Tumors

Chondroma—Were it not for the fact that certain of the benign tumors not only cause symptoms that require relief but also exhibit a definite tendency to undergo malignant transformation it would often be permissible to leave them untreated. This policy however is not without risk and we have seen a considerable group in which secondary or late sarcomatous development has taken place. This is true both of the central or enchondroma tnd the osteochondroma, although we have never seen malignant degeneration in chondroma of a phalanx. It is therefore a real responsibility to decide whether or not to employ surgery in a given case. In general the accessible lesions are removed surgically; this is true particularly of the central chondroma. If the decision is not to operate then the patient must be kept under observation for an indefinite period and warned to report at once any change in the size of the tumor or any increase of symptoms.

Clean and complete extirpation of the entire area of involvement is all that is required. Central chondromas may be carefully curetted and the resulting cavity then treated with an escharotic, such as zinc chloride, following which it may be filled with bone taken from the ilium or the tibia. Osteochondromas should be removed completely leaving a base of normal bone. Incomplete removal is hazardous. Chondromas of the pelvic bones constitute a distinct problem due to the difficulty of complete extirpation.

Bone Cyst and Giant Cell Tumor—These two conditions are considered together not only because they have many features in common but because their surgical management is essentially the same. Thorough curettage through a window wide enough to give good exposure and adequate access to all parts of the tumor is usually curative. However bone regeneration in the destroyed area is facilitated and made more certain if transplants of strips of cortical bone from the tibia, or chips of cancellous bone from the iliac crest are used to fill the cavity. Here also an escharotic solution is generally used to swab the lining of the cavity prior to closure of the wound in layers without drainage or packing. Primary wound closure as we have often emphasized is a matter of paramount importance. Giant cell tumors located in the rib, fibula, or patella may be dealt with by resection of the entire tumor-bearing area with assurance against recurrence. In the upper tibia and

lower femur, where the majority of these tumors are found, curettage may in 10 or 15 per cent of cases be followed by a recurrence. In some of these cases a second curettage is essential but in others, due to an accompanying change in the cellularity of the tissue, successive attempts at removal are unsuccessful and end with a definite sarcomatous alteration. In such cases even amputation may fail to prevent death from pulmonary metastasis. Fortunately these tragic consequences are infrequent nor are they confined to cases managed by surgery but at times may follow roentgen therapy. Solitary bone cyst responds more uniformly to curettage than does giant cell tumor; recurrences are less frequent and less serious since most of them yield to a second curettage; we have yet to see an example of late malignant transformation in a case treated by surgery alone. However, we have records of three instances of sarcoma developing from 13 to 15 years after roentgen therapy.

Malignant Tumors

Osteogenic Sarcoma: By far the greater proportion of cases of osteogenic sarcoma of long bones offers little or no opportunity for conservative surgery and amputation is admittedly the only course open to the surgeon. Inasmuch as the average practitioner sees so few of these cases he is apt to accept the pessimistic views of those who contend that amputation is nearly always followed by a fatal outcome. I am opposed to this defeatist attitude and wish to express a different view.

In a series of histologically confirmed cases treated at Memorial Hospital from 1917 to 1940 the survival rate for osteogenic sarcoma was 21.8 per cent. We have records of 56 patients who have survived for five or more years and only five of them died subsequently of sarcoma. Of these 56 patients 16 were well for more than ten years. Moreover considering only those cases regarded as suitable for amputation, Pool and I found the five-year survival rate in a series of 89 amputations to be 32 per cent. This would seem a worthwhile salvage in a disease that is regarded by some to be nearly always fatal.

It has been stated that amputation for osteogenic sarcoma ought always to be performed proximal to the bone involved rather than through it. This rule seems at first glance entirely logical but it involves a hip-joint disarticulation in cases of sarcoma of the lower femur which, incidentally, is the most frequent site of the disease. In our experience

few patients have been able to get about with any degree of satisfaction using a hip-joint prosthesis. Therefore for the past twenty years we have been practicing high thigh amputation in cases in which the character and extent of the tumor seemed to warrant it. Our results prompt us to recommend it as a substitute for routine disarticulation at the hip in cases in which clinical and roentgenographic examination show the tumor to be confined to the lower third of the femur. The level of amputation in such cases varies but it is always at least as high as the junction of the upper fourth and lower three-fourths of the bone.

In order to ascertain the risk involved in amputating through the affected bone rather than proximal thereto a survey was made of 40 consecutive cases in which this procedure was adopted. In 39 cases the lesion involved the lower femur and in one, the lower fibula. Stump-recurrence took place in only two instances or in 5 per cent, but in one of these a secondary hip disarticulation was followed by a five-year survival. Hence it is assumed that a hip disarticulation was avoided in 38 cases only to have one in which such a procedure might perhaps have succeeded. The five-year survival rate in these 40 cases was 14 or 35 per cent. This is slightly better than the figure reported by Pool and myself for 89 unselected amputations. This survey seems to offer conclusive evidence that, with due regard to the selection of cases, the principle of avoiding the more mutilating operation of hip-joint disarticulation is a sound one.

In exceptional circumstances a less radical procedure than amputation may be attempted. For selected cases of chondrosarcoma of the scapula a total scapulectomy is as satisfactory as is an interscapulothoracic disarticulation and it preserves a useful upper extremity. Segmental resection of the tumor-bearing area of a long bone supplemented by massive bone graft is a valuable means of avoiding amputation; this method may be used more extensively as our experience with it increases. Phemister has even resected a segment of the femur for central sarcoma and substituted therefor grafts from both tibiae with an excellent result.

Endothelioma–Ewing's Sarcoma of Bone: The widely held belief that Ewing's sarcoma of bone (endothelioma) is highly radiosensitive is probably based upon the prompt relief of pain and disappearance of the swelling followed by reparative changes in the bone which accompany even small doses of roentgen therapy. However, Woodard and

I have found that results are quite variable for long-term control of the local lesion. We feel that tissue doses as high as from 3000 to 5000 *r* can be expected to control the growth in about 50 per cent of these cases, and that doses in excess of 6000 *r* may be required to sterilize the tumor permanently. Such huge doses can be expected to cause complete loss of the normal regenerative powers of bone.

We believe therefore that it is worthwhile in cases with a favorable setting to attempt a resection of the tumor-bearing portion of the bone after a moderate course of preliminary radiation. We have several patients who have survived for long periods following the employment of this method. Unfortunately opportunities to utilize this combined attack are not often encountered.

It is our opinion that before resorting to any form of treatment for Ewing's sarcoma, a microscopic diagnosis should be made since even small doses of roentgen-rays may so alter the histologic appearance of the disease as to prevent the pathologist from identifying the tissue subsequently removed as *endothelioma.* In such instances, a diagnosis of "inflammatory process" is usually rendered and treatment is either suspended entirely or is undertaken with the misconception that one is dealing with an infection rather than a sarcoma.

Plasma Cell Myeloma: This uniformly fatal disease offers few opportunities for surgical treatment because of its polyostotic distribution. Aspiration biopsy is generally a satisfactory substitute for open biopsy. However if for any reason, aspiration is not considered advisable, surgical biopsy is applicable.

Reticulum Cell Sarcoma Primary in Bone: Since Parker and Jackson first described this tumor in 1939 we have encountered only 11 cases which seemed to fulfill the necessary criteria. We would emphasize that while histologically there is a close resemblance to Ewing's sarcoma the roentgenographic appearance is not typical of the latter disease. The tumor is radiosensitive and our experience leads us to regard radiation therapy as the method of choice. Amputation can usually be avoided; therefore when a surgical biopsy results in a definite diagnosis of reticulum cell sarcoma it is proper to regard further surgery as seldom indicated.

Liposarcoma of Bone: There is as yet no widespread acceptance of the theory that primary liposarcoma of bone is a definite entity. Long survival after amputation in a few cases in which this diagnosis has been

made, however, prompts us to recommend it as an appropriate method of treatment. There is some evidence however that these extremely rare tumors are radiosensitive.

Palliative surgery for metastatic tumors of bone and inoperable sarcoma: It is well to recognize the fact that bone metastasis from cancer primary in other organs constitutes a numerically greater proportion of all skeletal malignant disease than does any of the bone sarcomas. Among the cancers which have a predilection for osseous involvement the following predominate: breast, prostate, kidney, thyroid and lung. It has been found impossible to effect a cure once bone metastasis has occurred. This being the case there is little place for surgery in the treatment of these unfortunate patients. Occasionally one encounters a case with marked involvement of a major long bone which histologically has been established as metastatic cancer and yet a painstaking search has failed to disclose the primary tumor or any other evidence of metastasis elsewhere, and the general health of the patient is excellent. This situation poses a problem in choice of treatment. One may elect to irradiate the part or to perform an amputation. If the pain is severe and a pathologic fracture is impending then removal of the limb may be followed in some instances by a long period of wellbeing and comfort. Before resorting to amputation in such cases it is imperative to obtain roentgenograms of the entire skeleton and to examine the patient thoroughly in the hope of discovering a primary growth. We have a few cases of palliative amputation in which the result obtained seems to have justified the procedure.

We are even more strongly convinced that patients with painful primary sarcomas, especially of the osteogenic and chondrosarcoma types, are made much more comfortable when, despite the presence of demonstrable metastatic lesions in the lungs, the offending member is amputated. This is a humane procedure.

Among the most difficult cases to manage are those with bulky, slowly-growing tumors of the pelvic bones. These radioresistant lesions include the chondromyxosarcomas and the sacral chordomas which seldom terminate in early metastasis but which wear the patient down by the effects of constant, excruciating pain. In such situations any form of radical surgery that offers the slightest prospect of eradication of the disease is justifiable; this includes even hemipelvectomy. Where no form of surgical extirpation is possible we have found that spinothalamic

cordotomy has given a large measure of relief providing it has been performed before the patient has had opiates. The latter counteract the beneficent effects of the surgical procedure by leading to demoralization which may ultimately cause the patient and his family as great distress as the pain itself.

Summary

Benign tumors of bone require surgical treatment not only for the present symptoms but for future malignant potentialities. The form of therapy differs with the type, the extent and the location of the tumor but seldom should amputation be required.

Surgery is also indicated for malignant tumors of bone. This implies amputation in most instances particularly for those types that are radio-resistant.

High thigh amputation for tumors of the lower femur has proved an acceptable substitute for routine hip-joint disarticulation. For tumors in other situations, amputation proximal to the bone involved is generally advisable although exceptions exist.

Under certain conditions and in special locations malignant tumors may be dealt with successfully by conservative surgical measures such as local excision, resection, curettage, scapulectomy, patellectomy, etc., rather than by amputation.

Judgment born of experience is of inestimable value in the selection of the method of treatment best adapted to the individual case.

REFERENCES

1. Coley, B. L. and Higinbotham, N. L. Surgical treatment of giant cell tumor, *Ann. Surg.*, 1936, *103*:821.
2. Coley, B. L. and Higinbotham, N. L. Solitary bone cyst; the localized form of osteitis fibrosa cystica, *Ann. Surg.*, 1934, *99*:432.
3. Coley, B. L. and Pool, J. L. Factors influencing the prognosis in osteogenic sarcoma, *Ann. Surg.*, 1940, *112*:1114.
4. Pack, G. T. and Ehrlich, H. E. Exarticulation of the lower extremities for malignant tumors, *Ann. Surg.*, 1946, *123*:1047; *124*:1.
5. Phemister, D. B. Rapid repair of defect of femur by massive bone grafts after resection for tumors, *Surg., Gynec. & Obst.*, 1945, *60*:120.
6. Parker, F., Jr. and Jackson, H., Jr. Primary reticulum cell sarcoma of bone, *Surg., Gynec. & Obst.*, 1939, *68*:45.
7. Stewart, F. W. Primary liposarcoma of bone, *Am. J. Path.*, 1931, *7*:87.

Emanuel Libman
1872-1946

Dr. Emanuel Libman passed away at the Mount Sinai Hospital on June 28, 1946, after a brief illness. Throughout his professional career he had devoted himself whole-heartedly to medical science and research, to medical practice of a high order, to the study of medical literature, to medical education and to promoting in others those ideals which had inspired his own life.

Libman was born on August 22, 1872, in New York City; he was graduated from the College of the City of New York with the degree of A.B. in 1891, and from the College of Physicians and Surgeons of Columbia University in 1894. During his internship at the Mount Sinai Hospital he came under the influence of Dr. Abraham Jacobi and Dr. Henry Koplik, and at first planned to become a pediatrician. With this in mind he made a trip to Europe and studied bacteriology in Graz under Theodore Escherich who had discovered the colon bacillus. In only a few weeks' work in Professor Escherich's laboratory, he discovered the Streptococcus enteritis, and isolated this streptococcus from the patient's blood. This initial experimental research may account for Libman's subsequent extensive work in blood cultures, in the "General Infections," and in bacterial endocarditis. On his return to New York he was appointed assistant pathologist at the Mount Sinai Hospital, and from that time played a most important and vital role in the development of its laboratories, both routine and research.

In medical history his name will probably always be associated with endocarditis in general, with the bacteria-free stage of endocarditis and with his description with Dr. Benjamin Sacks of a new form of endocarditis which he called atypical verrucous endocarditis, now termed the Libman-Sacks disease.

Notable as were his achievements in bacteriology and pathology, he will be remembered by many physicians for his extraordinary knowledge of internal medicine and its literature, and his brilliance as a diagnostician. He had come under the influence of three great internists, Dr. Francis Delafield, Dr. Edward Gamaliel Janeway and Dr. William Osler, and at least some of his success was due to their fine example and teaching.

Important as his work was in the laboratory and at the bedside, of equal value were his interest and promotion of postgraduate medical education of others, especially of younger physicians. The outstanding characteristic of Libman was his ability to stimulate, to inspire, to quicken others to work and study with something of his own enthusiasm. He was instrumental in getting the initial funds for the work of the Committee on Medical Education at his hospital. He either himself endowed or helped in the establishment of the following funds, all for medical education or research:—the Edward Gamaliel Janeway Lectureship, the William Henry Welch Lectureship, a lectureship in honor of Hideyo Noguchi at the Johns Hopkins Hospital, the Humphrey Davy Rolleston Lectureship at The Royal College of Physicians in London, the Herbert Celler Fellowship Fund, and the Henry Dazian Foundation for Medical Research. The latter during the recent war provided fellowships for Latin-American doctors wishing to pursue research in this country. He was a great friend of, and liberal contributor to the Hebrew University in Palestine. It is not so well known that he left a contingent legacy in his will for the Tuskegee Institute of Alabama, probably as an expression of his own belief that "mankind should treat all races as one." The Libman Fellowship Fund was established by a number of his friends as a tribute to Libman for his work in postgraduate medical education.

He always enjoyed working at the Academy of Medicine. He was a leading spirit in the activities of the Committee on Medical Education of The New York Academy of Medicine from its incipiency to the last

year of his life when he reluctantly withdrew because of his failing health. The Graduate Fotrnights, originally suggested by Dr. Ludwig Kast, were always a challenge to him, and their success year after year was a source of great satisfaction, as he considered them a valuable means of teaching. He was one of the first, if not the first to form a group who demonstrated exhibits over and over again to successive audiences. The most perfect tribute to Libman, but necessarily incomplete, is the "Introduction" to the three Libman Anniversary Volumes, by his great friend, William H. Welch. In that introduction Dr. Welch writes: "An almost unsurpassed gift of Libman as a teacher is his skill in collecting material and in preparing exhibits of specimens and illustrations for his lectures and demonstrations. Many of his appearances, accompanied often by a group of his pupils to present a paper or exhibit at a meeting of medical societies or at international congresses have been notable events, never forgotten by the hearers. I doubt if there has ever before been assembled such an instructive and comprehensive exhibit of the cardiovascular system in all its aspects, anatomical, physiological, pathological, bacteriological and clinical, as that brought together under the supervision of Libman to illustrate the course of lectures and demonstrations of the Graduate Fortnight of the New York Academy of Medicine in October, 1931.

In addition to his formal work in medical education, he was tireless in his efforts to help younger physicians and scientists by his sound advice, his stimulation and his financial aid. As a result he built up a school of disciples and gathered a host of personal friends both here and abroad with whom he kept in touch to the end of his life.

Libman belonged to an age which is passing, but he saw clearly the age that is waiting before, and prepared others to meet the burden of the future. He was a scholar, an investigator, a fine physician and a philanthropist. He preached and practised the continued education of the physician throughout his own long and brilliant career in medicine. We who knew him will always cherish his memory.

BERNARD S. OPPENHEIMER.

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